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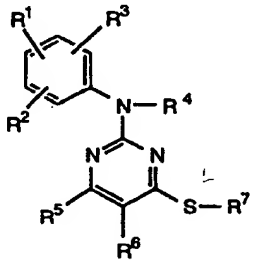

(1)

(57) Abstract

Compounds of formula (1) are described and the salts, solvates, hydrates and N-oxides thereof, in which R^1, R^2, R^3, R^4, R^5, R^6 and R^7 have the meanings given in Claim 1. The compounds are selective inhibitors of protein kinases, especially src-family protein kinases and are of use in the prophylaxis and treatment of immune diseases, hyperproliferative disorders and other diseases in which inappropriate protein kinase action is believed to have a role.

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SUBSTITUTED 2-ANILINOPYRIMIDINES USEFUL AS PROTEIN KINASE INHIBITORS

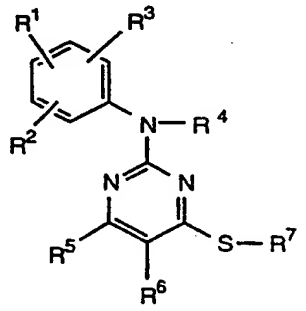
This invention relates to substituted 2-anilinopyrimidines, to processes for their preparation, to pharmaceutical compositions containing them, and to their use in medicine.

Protein kinases participate in the signalling events which control the activation, growth and differentiation of cells in response to extracellular mediators and to changes in the environment. In general, these kinases fall into two groups; those which preferentially phosphorylate serine and/or threonine residues and those which preferentially phosphorylate tyrosine residues [Hanks, S K, Hunter T, FASEB. J. 9, 576-596 (1995)]. The serine/threonine kinases include for example, protein kinase C isoforms [Newton A C, J. Biol. Chem. 270, 28495-28498 (1995)] and a group of cyclin-dependent kinases such as cdc2 [Pines J, Trends in Biochemical Sciences 18, 195-197 (1995)]. The tyrosine kinases include membrane-spanning growth factor receptors such as the epidermal growth factor receptor [Iwashita S and Kobayashi M. Cellular Signalling 4, 123-132 (1992)], and cytosolic non-receptor kinases such as ZAP-70 and csk kinases [Chan C *et al* Ann. Rev. Immunol. 12, 555-592 (1994)]. A particular group of non-receptor tyrosine kinases are a group known as the src family which includes $p56^{lck}$ and $p59^{fyn}$ [Kefelas P *et al* International Journal of Biochemistry and Cell Biology 27, 551-563 (1995)].

Inappropriately high protein kinase activity has been implicated in many diseases resulting from abnormal cellular function. This might arise either directly or indirectly, for example by failure of the proper control mechanisms for the kinase, related for example to mutation, over-expression or inappropriate activation of the enzyme; or by over- or underproduction of cytokines or growth factors also participating in the transduction of signal upstream or downstream of the kinase. In all of these instances, selective inhibition of the action of the kinase might be expected to have a beneficial effect.

We have now found a series of substituted 2-anilinopyrimidines which are potent and selective inhibitors of protein kinases, especially src-family protein kinases. The compounds are thus of use in the prophylaxis and treatment of immune diseases, hyperproliferative disorders and other diseases in which inappropriate protein kinase action is believed to have a role.

Thus, according to one aspect of the invention, we provide a compound of formula (1):



(1)

wherein R^1 is a $-XR^8$ group [where X is a covalent bond, -O-, -S-, -C(O)-, -C(S)-, -C(O)O-, -S(O)-, $-S(O_2)-$, $-CH_2-$, -or $N(R^9)-$ [where R^9 is a hydrogen atom or a straight or branched alkyl group] and R^8 is a hydrogen atom or an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group], or a $-NO_2$, -CN, $-SO_2NH_2$, $-SO_2NHR^8$, $-SO_2N(R^8)_2$ [where each R^8 group may be the same or different], $-CONH_2$, $-CONHR^8$, $-CON(R^8)_2$ [where each R^8 group may be the same or different], $-CSNH_2$, $-CSNHR^8$, $-CSN(R^8)_2$ [where each R^8 group may be the same or different], $-NH_2$ or substituted amino group;

R^2 and R^3 which may be the same or different is each a hydrogen or halogen atom or a group selected from an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, -OH, $-OR^{10}$ [where R^{10} is an optionally substituted aliphatic group], $-OR^{10a}$ [where R^{10a} is an optionally substituted cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group] -SH, $-NO_2$, -CN, $-SR^8$, $-COR^8$, $S(O)R^8$,

$-SO_2R^8$, $-SO_2NH_2$, $-SO_2NHR^8$, $-SO_2N(R^8)_2$ [where each R^8 group may be the same or different] $-CO_2H$, $-CO_2R^8$, $-CONH_2$, - $CONHR^8$, $-CON(R^8)_2$, [where each R^8 group may be the same or different] $-CSNH_2$, $-CSNHR^8$, $-CSN(R^8)_2$, [where each R^8 group may be the same or different] $-NH_2$ or substituted amino group provided that when one or both of R^2 and R^3 is an $-OR^{10}$ group then R^1 is an $-OR^8$ group in which R^8 is an optionally substituted cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group or an aliphatic group substituted by a cyclic amino group;

R^4 is a hydrogen atom or a straight or branched alkyl group;

R^5 is a hydrogen atom or an optionally substituted straight or branched alkyl, alkenyl or alkynyl group;

R^6 is a hydrogen or halogen atom or an amino, substituted amino, nitro, $-CO_2H$, or $-CO_2R^8$ group or a group $-X^1-R^{6a}$ where X^1 is a direct bond or a linker atom or group and R^{6a} is an optionally substituted straight or branched alkyl, alkenyl or alkynyl group;

R^7 is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group; and the salts, solvates, hydrates and N-oxides thereof.

When in the compounds of formula (1) X^1 is present as a linker atom or group it may be for example an -O- or -S- atom or a -C(O)-, -C(S)-, -S(O)-, $-S(O)_2-$, $-N(R^{11})-$ [where R^{11} is a hydrogen atom or a C_{1-6} alkyl, e.g. methyl or ethyl, group], $-CON(R^{11})-$, $-OC(O)N(R^{11})-$, $-CSN(R^{11})-$, $-N(R^{11})CO-$, $-N(R^{11})C(O)O-$, $-N(R^{11})CS-$, $-SON(R^{11})$, $-SO_2N(R^{11})$, $-N(R^{11})SO_2-$, $-N(R^{11})CON(R^{11})-$, $-N(R^{11})CSN(R^{11})-$, $-N(R^{11})SON(R^{11})-$ or $-N(R^{11})SO_2N(R^{11})$ group.

In the compounds of formula (1), when R^1 is $-XR^8$ and R^8 is an optionally substituted aliphatic group, R^8 may be an optionally substituted C_{1-10} aliphatic group for example an optionally substituted straight or branched chain C_{1-6} alkyl, e.g. C_{1-3} alkyl, C_{2-6} alkenyl, e.g. C_{2-4} alkenyl, or C_{2-6} alkynyl, e.g. C_{2-4} alkynyl group. Each of said groups may be optionally interrupted by one or two heteroatoms or heteroatom-containing groups represented by X^2 [where X^2 is an atom or group as just described for X^1], to form an optionally substituted R^8 heteroaliphatic group.

Particular examples of aliphatic groups represented by R^8 include optionally substituted $-CH_3$, $-CH_2CH_3$, $-(CH_2)_2CH_3$, $-CH(CH_3)_2$, $-(CH_2)_3CH_3$, $-CH(CH_3)CH_2CH_3$, $-CH_2CH(CH_3)_2$, $-C(CH_3)_3$, $-(CH_2)_4CH_3$, $-(CH_2)_5CH_3$, $-CHCH_2$, $-CHCHCH_3$, $-CH_2CHCH_2$, $-CHCHCH_2CH_3$, $-CH_2CHCHCH_3$, $-(CH_2)_2CHCH_2$, $-CCH$, $-CCCH_3$, $-CH_2CCH$, $-CCCH_2CH_3$, $-CH_2CCCH_3$, or $-(CH_2)_2CCH$ groups. Where appropriate each of said groups may be optionally interrupted by one or two atoms and/or groups X^2 to form an optionally substituted heteroaliphatic group. Particular examples include $-CH_2X^2CH_3$, $-CH_2X^2CH_2CH_3$, $-(CH_2)_2X^2CH_3$ and $-(CH_2)_2X^2CH_2CH_3$ groups.

The optional substituents which may be present on these aliphatic and/or heteroaliphatic groups include one, two, three or more substituents selected from halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or hydroxyl, C_{1-6} alkoxy, e.g. methoxy or ethoxy, thiol, C_{1-6} alkylthio e.g. methylthio or ethylthio, $-SC(NH)NH_2$, $-CH_2C(NH)NH_2$, amino, substituted amino or cyclic amino groups.

Substituted amino groups include for example groups of formulae $-NR^9R^{10}$ [where R^9 is an optionally substituted C_{1-6} alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl group optionally interrupted by one or two heteroatoms or heteroatom-containing groups represented by X^3 (where X^3 is an atom or group as described above for X^1) and R^{10} is a hydrogen atom or is a group as just defined for R^9], $-N(R^{10})COR^9$, $-N(R^{10})CSR^9$, $-N(R^{10})SOR^9$, $-N(R^{10})SO_2R^9$, $-N(R^{10})CONH_2$, $-N(R^{10})CONR^9R^{10}$, $-N(R^{10})C(O)OR^9$, $-N(R^{10})C(NH)NH_2$, $-N(R^{10})C(NH)NR^9NR^{10}$, $-N(R^{10})CSNH_2$, $-N(R^{10})CSNR^9R^{10}$, $-N(R^{10})SONH_2$, $-N(R^{10})SONR^9R^{10}$, $-N(R^{10})SONH_2$, $-N(R^{10})SO_2NH_2$, $-N(R^{10})SONR^9R^{10}$, or $-N(R^{10})Cyc^1$ [where Cyc^1 is an optionally substituted C_{3-7} monocyclic carbocyclic group optionally containing one or more -O- or -S- atoms or $-N(R^{11})-$, -C(O)-, -C(S)-. -S(O)- or $-S(O_2)-$ groups].

Cyclic amino substituents which may be present on R^8 aliphatic or heteroaliphatic groups include groups of formula $-NHet^1$, where $-NHet^1$ is

an optionally substituted C_{3-7} cyclic amino group optionally containing one or more other heteroatoms or heteroatom containing groups selected from -O- or -S- atoms -N(R^{11})-, -C(O), -C(S)-, -S(O)- or -S(O_2)- groups.

Particular examples of amino, substituted amino and cyclic amino groups include -NH_2, methylamino, ethylamino, dimethylamino, diethylamino, -NHCyc^1 where Cyc^1 is an optionally substituted cyclopentyl, cyclohexyl, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, piperazinyl or thiomorpholinyl group, or -NHHet^1 where -NHHet^1 is an optionally substituted pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, morpholinyl, piperazinyl or thiomorpholinyl group. Optional substituents which may be present on these groups and substituted and cyclic amino groups in general include one, two or three halogen atoms, e.g. fluorine, chlorine, bromine or iodine atoms, or C_{1-4}alkyl, e.g. methyl or ethyl, hydroxyl, or C_{1-4}alkoxy, e.g. methoxy or ethoxy groups.

When R^8 is present in compounds of formula (1) as an optionally substituted cycloaliphatic group it may be an optionally substituted C_{3-10} cycloaliphatic group. Particular examples include optionally substituted C_{3-10}cycloalkyl, e.g. C_{3-7}cycloalkyl, or C_{3-10}cycloalkenyl e.g. C_{3-7}cycloalkenyl groups.

Heteroaliphatic or heterocycloaliphatic groups represented by R^8 include the aliphatic or cycloaliphatic groups just described for R^8 but with each group additionally containing one, two, three or four heteroatoms or heteroatom-containing groups represented by X^2, where X^2 is as described above.

Particular examples of R^8 cycloaliphatic and heterocycloaliphatic groups include optionally substituted cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, 2-cyclobuten-1-yl, 2-cyclopenten-1-yl, 3-cyclopenten-1-yl, 2,4-cyclopentadien-1-yl, 3,5,-cyclohexadien-1-yl, tetrahydrofuranyl, pyrroline, e.g. 2- or 3-pyrrolinyl, pyrrolidinyl, dioxolanyl, e.g. 1,3-dioxolanyl, imidazolinyl, e.g. 2-imidazolinyl, imidazolidinyl, pyrazolinyl, e.g. 2-pyrazolinyl, pyrazolidinyl, pyranyl, e.g. 2- or 4-pyranyl, piperidinyl, 1,4-dioxanyl, morpholinyl, 1,4-dithianyl, thiomorpholinyl,

piperazinyl, 1,3,5-trithianyl, oxazinyl, e.g. 2H-1,3-, 6H-1,3-, 6H-1,2-, 2H-1,2- or 4H-1,4- oxazinyl, 1,2,5-oxathiazinyl, isoxazinyl, oxathiazinyl, e.g. 1,2,5 or 1,2,6-oxathiazinyl, or 1,3,5-oxadiazinyl groups.

Optional substituents which may be present on R^8 cycloaliphatic and heterocycloaliphatic groups include those optional substituents described above for R^8 when it is an aliphatic group. The heterocycloaliphatic groups may be attached to the remainder of the molecule of formula (1) through any appropriate ring carbon or heteroatom.

When R^8 is present as an aromatic group in compounds of formula (1) it may be for example an optionally substituted monocyclic or bicyclic fused ring C_{6-12} aromatic group, such as an optionally substituted phenyl, 1- or 2-naphthyl, 1- or 2-tetrahydronaphthyl, indanyl or indenyl group.

Heteroaromatic groups represented by R^8 include optionally substituted C_{1-9} heteroaromatic groups containing for example one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. In general, the heteroaromatic groups may be for example monocyclic or bicyclic fused ring heteroaromatic groups. Monocyclic heteroaromatic groups include for example five- or six-membered heteroaromatic groups containing one, two, three or four heteroatoms selected from oxygen, sulphur or nitrogen atoms. Bicyclic heteroaromatic groups include for example nine- to thirteen-membered fused-ring heteroaromatic groups containing one, two or more heteroatoms selected from oxygen, sulphur or nitrogen atoms.

Examples of heteroaromatic groups represented by R^8 include optionally substituted pyrrolyl, furyl, thienyl, imidazolyl, N-methylimidazolyl, N-ethylimidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, pyrazolyl, 1,2,3-triazolyl, 1,2,4-triazolyl, 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl, 1,2,5-oxadiazolyl, 1,3,4-oxadiazolyl, 1,3,4-thiadiazole, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, 1,3,5-triazinyl, 1,2,4-triazinyl, 1,2,3-triazinyl, benzofuryl, [2,3-dihydro]benzofuryl, isobenzofuryl, benzothienyl, benzotriazolyl, isobenzothienyl, indolyl, isoindolyl, benzimidazolyl, imidazo[1,2-a]pyridyl, benzothiazolyl, benzoxazolyl, benzopyranyl, [3,4-

dihydro]benzopyranyl, quinazolinyl, naphthyridinyl, pyrido[3,4-b]pyridyl, pyrido[3,2-b]pyridyl, pyrido[4,3-b]pyridyl, quinolinyl, isoquinolinyl, tetrazolyl, 5,6,7,8-tetrahydroquinolinyl, 5,6,7,8-tetrahydroisoquinolinyl, and imidyl, e.g. succinimidyl, phthalimidyl, or naphthalimidyl such as 1,8-naphthalimidyl.

Optional substituents which may be present on any of the above armoatic or heteroaromatic groups in compounds of formula (1) include one, two, three or more substituents, each represented by the group R^{12}. The substituent R^{12} may be selected from an atom or group R^{13} or $-Alk(R^{13})_m$, where R^{13} is a halogen atom, or an amino ($-NH_2$), $-NHR^{14}$ [where R^{14} is an $-Alk(R^{13})_m$, heterocycloalkyl, -Alk-heterocycloalkyl, aryl or heteroaryl group], $-N(R^{14})_2$ [where each R^{14} group is the same or different], nitro, cyano, hydroxyl (-OH), $-OR^{14}$, formyl, carboxyl ($-CO_2H$), esterified carboxyl, thiol (-SH), $-SR^{14}$, $-COR^{14}$, $-CSR^{14}$, $-SO_3H$, $-SO_2R^{14}$, $-SO_2NH_2$, $-SO_2NHR^{14}$, $SO_2N[R^{14}]_2$, $-CONH_2$, $-CSNH_2$, $-CONHR^{14}$, $-CSNHR^{14}$, $-CON[R^{14}]_2$, $-CSN[R^{14}]_2$, $-N(R^{11})SO_2H$ [where R^{11} is as defined above], $-N(R^{11})SO_2R^{14}$, $-N[SO_2R^{14}]_2$, $-N(R^{11})SO_2NH_2$, $-N(R^{11})SO_2NHR^{14}$, $-N(R^{11})SO_2N[R^{14}]_2$, $-N(R^{11})COR^{14}$, $-N(R^{11})CONH_2$, $-N(R^{11})CONHR^{14}$, $-N(R^{11})CON[R^{14}]_2$, $-N(R^{11})CSR^{14}$, $-N(R^{11})CSNH_2$, $-N(R^{11})CSNHR^{14}$, $-N(R^{11})CSN[R^{14}]_2$, $-N(R^{11})C(O)OR^{14}$, or an optionally substituted cycloalkyl, aryl or heteroaryl group; Alk is a straight or branched C_{1-6} alkylene, C_{2-6} alkenylene or C_{2-6} alkynylene chain, optionally interrupted by one, two or three -O- or -S- atoms or S-(O)-, $-S(O)_2-$ or $-N(R^{11})-$ groups; and m is zero or an integer 1, 2 or 3.

When in the group $-Alk(R^{13})_m$ m is an integer 1, 2 or 3, it is to be understood that the substituent or substituents R^{13} may be present on any suitable carbon atom in -Alk. Where more than one R^{13} substituent is present these may be the same or different and may be present on the same or different atom in -Alk or in R^7 as appropriate. Thus for example, R^7 may represent a $-CH(R^{13})_2$ group, such as a -CH(OH)Ar group where Ar is an aryl or heteroaryl group as defined below. Clearly, when m is zero and no substituent R^{13} is present the alkylene, alkenylene or alkynylene chain represented by Alk becomes an alkyl, alkenyl or alkynyl group.

When R^{13} is a halogen atom it may be for example a fluorine, chlorine, bromine, or iodine atom.

Esterified carboxyl groups represented by the group R^{13} include groups of formula $-CO_2Alk^1$ wherein Alk^1 is a straight or branched, optionally substituted C_{1-8} alkyl group such as a methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl, s-butyl or t-butyl group; a $C_{6-12}arylC_{1-8}alkyl$ group such as an optionally substituted benzyl, phenylethyl, phenylpropyl, 1-naphthylmethyl or 2-naphthylmethyl group; a $C_{6-12}aryl$ group such as an optionally substituted phenyl, 1-naphthyl or 2-naphthyl group; a $C_{6-12}aryloxyC_{1-8}alkyl$ group such as an optionally substituted phenyloxymethyl, phenyloxyethyl, 1-naphthyloxymethyl, or 2-naphthyloxymethyl group; an optionally substituted $C_{1-8}alkanoyloxyC_{1-8}alkyl$ group, such as a pivaloyloxymethyl, propionyloxyethyl or propionyloxypropyl group; or a $C_{6-12}aroyloxyC_{1-8}alkyl$ group such as an optionally substituted benzoyloxyethyl or benzoyloxypropyl group. Optional substituents present on the Alk^1 group include R^{13} substituents described above.

When Alk is present in or as a substituent R^{12} it may be for example a methylene, ethylene, n-propylene, i-propylene, n-butylene, i-butylene, s-butylene, t-butylene, ethenylene, 2-propenylene, 2-butenylene, 3-butenylene, ethynylene, 2-propynylene, 2-butynylene or 3-butynylene chain, optionally interrupted by one, two, or three -O- or -S-, atoms or $-S(O)-$, $-S(O)_2-$ or $-N(R^{11})-$ groups.

Optionally substituted cycloalkyl groups represented by the group R^{13} include optionally substituted C_{5-7} cycloalkyl groups such as optionally substituted cyclopentyl or cyclohexyl groups.

Heterocycloalkyl groups represented by the group R^{12} or R^{14} include optionally substituted $heteroC_{3-6}cycloalkyl$ groups containing one or two oxygen, sulphur or nitrogen atoms. Particular examples of such groups include optionally substituted azetidinyl pyrrolidinyl, piperidinyl, piperazinyl, homopiperazinyl, morpholinyl or thiomorpholinyl groups. The heterocycloalkyl group may be attached to the remainder of the molecule through any of its ring carbon atoms, or where present, ring nitrogen atom. Where the

group R^{12} is an -Alk-heterocycloalkyl group, Alk may be as defined above and the heterocycloalkyl portion may be as just defined, attached to Alk through any of its ring carbon atoms, or where present, ring nitrogen atom.

Optional subsituents which may be present on R^{12}, R^{13} or R^{14} cycloalkyl or heterocycloalkyl groups include one or two C_{1-6} alkyl, e.g. methyl or ethyl, hydroxyl (-OH) hydroxyC_{1-6}alkyl, e.g. hydroxymethyl or hydroxyethyl, or C_{1-6} alkoxy, e.g. methoxy or ethoxy groups. The substituent(s) may be present on any available ring carbon or nitrogen atom as appropriate.

Aryl and heteroaryl groups represented by the groups R^{13} or R^{14} include for example optionally substituted monocyclic or bicyclic C_{6-12} aromatic groups, or C_{1-9} heteroaromatic groups such as those described above in relation to the group R^8.

Particularly useful atoms or groups represented by R^{12} include fluorine, chlorine, bromine or iodine atoms, or C_{1-6}alkyl, C_{1-6} alkylamino, C_{1-6} hydroxyalkyl, C_{1-6}alkylthiol, C_{1-6}alkoxy, hydroxyC_{1-6}alkoxy, aminoC_{1-6} alkoxy, C_{1-6}alkylaminoC_{1-6}alkoxy, C_{1-6}dialkylaminoC_{1-6}alkoxy, optionally substituted C_{5-7}cyclo-alkoxy, optionally substituted C_{5-7}cycloalkyl, optionally substituted C_{5-7}cycloalkylamino, haloC_{1-6}alkyl, haloC_{1-6}alkoxy, C_{1-6}alkylamino, amino (-NH_2), aminoC_{1-6}alkyl, C_{1-6}dialkylamino, hydroxyC_{1-6} alkylamino, aminoC_{1-6}alkylamino, C_{1-6}alkylaminoC_{1-6}alkyl-amino, C_{1-6}dialkylaminoC_{1-6}alkylamino, C_{1-6}alkylaminoC_{1-6} dialkylamino, C_{1-6}dialkylaminoC_{1-6}dialkylamino, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO_2H), -CH_2CO_2H, -OCH_2CO_2H, -CO_2Alk^1 [where Alk^1 is as defined above], -$CH_2CO_2Alk^1$, C_{1-6}alkoxycarbonylC_{1-6}alkoxy, C_{1-6} alkanoyl, optionally substituted phenyl C_{1-6}alkanoyl, thiol (-SH), thioC_{1-6}alkyl, -SC(NH)NH_2, sulphonyl (-SO_3H), C_{1-6}alkylsulphonyl, optionally substituted phenylsulphonyl, aminosulphonyl (-SO_2NH_2), C_{1-6}alkylaminosulphonyl, C_{1-6}dialkylaminosulphonyl, optionally substituted phenylamino-sulphonyl, carboxamido (-$CONH_2$), C_{1-6}alkyl-aminocarbonyl, C_{1-6}dialkylaminocarbonyl, optionally substituted phenyl-aminocarbonyl, aminocarbonylmethyl, C_{1-6}alkylaminocarbonylmethyl, optionally substituted benzylaminocarbonylmethyl, -NHC(S)NH_2, sulphonyl-amino (-$NHSO_2H$), C_{1-6}alkylsulphonylamino, C_{1-6}dialkylsulphonylamino, optionally substituted

phenylsulphonylamino, aminosulphonylamino (-$NHSO_2NH_2$), C_{1-6}alkylaminosulphonylamino, C_{1-6}dialkylaminosulphonylamino, optionally substituted phenylaminosulphonylamino, aminocarbonyl-amino, C_{1-6}alkylaminocarbonylamino C_{1-6}dialkylaminocarbonylamino, phenylaminocarbonylamino, C_{1-6}alkanoylamino, aminoC_{1-6} alkanoylamino, optionally substituted pyridylcarboxyamino, C_{1-6}alkanoylaminoC_{1-6}alkyl, C_{1-6}alkoxycarbonylamino, optionally substituted heteroC_{3-6}cycloalkyl, piperidinyl, piperazinyl, 4-methylpiperazinyl, homopipeprazinyl, or morpholinyl, optionally substituted heteroC_{3-6}cycloalkylC_{1-6}alkyl, piperidinylC_{1-6}alkyl, piperazinylC_{1-6}alkyl or morpholinylC_{1-6}alkyl, optionally substituted heteroC_{3-6}alkylC_{1-6}alkylamino, optionally substituted heteroC_{3-6}cycloalkylamino, tetrazolyl, optionally substituted phenylamino, optionally substituted benzylamino, optionally substituted benzyloxy, or optionally substituted pyridiylmethylamino group.

Where desired, two R^{12} substituents may be linked together to form a cyclic group such as a cyclic ether, e.g. a C_{1-6}alkylenedioxy group such as a methylenedioxy or ethylenedioxy group.

Especially useful R^{12} substituents include for example fluorine, chlorine, bromine or iodine atoms, or a methylamino, ethylamino, hydroxymethyl, hydroxyethyl, methylthiol, ethylthiol, methoxy, ethoxy, n-propoxy, 2-hydroxyethoxy, 3-hydroxypropoxy, 4-hydroxybutoxy, 2-aminoethoxy, 3-aminopropoxy, 2-(methylamino)ethoxy, 2-(dimethylamino)ethoxy, 3-(dimethylamino)propoxy, cyclopentyloxy, cyclohexyl, cyclohexylamino, 2-hydroxycyclohexylamino, trifluoromethyl, trifluoromethoxy, methylamino, ethylamino, amino (-$NH)_2$, aminomethyl, aminoethyl, dimethylamino, diethylamino, ethyl(methyl)amino, propyl(methyl)amino, 2-hydroxyethylamino, 3-hydroxypropylamino, 4-hydroxybutylamino, 2-aminoethylamino, 3-aminopropylamino, 4-aminobutylamino, 2-(methylamino)ethylamino, 2-(ethylamino)ethylamino, 2-(i-propylamino)ethylamino, 3-(i-propylamino)-propylamino, 2-(dimethylamino)ethylamino, 3-(dimethylamino)propylamino, 2-(diethylamino)ethylamino, 3-(diethylamino)propylamino, 2-(methylamino)-ethyl(methyl)amino, 3-(methylamino)propyl(methyl)amino, 2-(dimethylamino)ethyl(methyl)amino, 2-(dimethylamino)ethyl(ethyl)amino, nitro, cyano, hydroxyl (-OH), formyl [HC(O)-], carboxyl (-CO_2H), -CH_2CO_2H, --

OCH_2CO_2H, $-CO_2CH_3$, $-CO_2CH_2CH_3$, $-CH_2CO_2CH_3$, $-CH_2CO_2CH_2CH_3$, $-CH_2CO_2CH_2$phenyl, t-butoxycarbonylmethoxy, acetyl, phenacetyl, thio (-SH), thiomethyl, thioethyl, $-SC(NH)NH_2$, sulphonyl ($-SO_2H$), methylsulphonyl, methylaminosulphonyl, ethylaminosulphonyl, dimethylaminosulphonyl, diethylaminosulphonyl, carboxamido ($-CONH_2$), methylaminocarbonyl, ethylaminocarbonyl, dimethylaminocarbonyl, diethylaminocarbonyl, methylaminocarbonylmethyl, $-NHC(S)NH_2$, sulphonylamino ($-NHSO_2H$), methylsulphonylamino ethylsulphonylamino, dimethylsulphonylamino, diethylsulphonylamino, sulphonylamino ($-NHSO_2NH_2$), methylaminosulphonylamino, ethylaminosulphonylamino, dimethylaminosulphonylamino, diethylaminosulphonylamino, methylaminocarbonylamino, ethylaminocarbonylamino, dimethylaminocarbonylamino diethylaminocarbonylamino, acetylamino, aminomethylcarbonylamino, acetylaminomethyl, methoxycarbonylamino, ethoxycarbonylamino, t-butoxycarbonylamino, pyrrolidinyl, piperidinyl, piperazinyl, 4-methylpiperazinyl, homopipeprazinyl, morpholinyl, pyrrolidinylC_{1-6}alkyl, piperidinylC_{1-6}alkyl, piperazinylC_{1-6}alkyl, morpholinylC_{1-6}alkyl, 2-pyrrolidinylethylamino, 2-(1-methylpyrrolidinyl)ethylamino, 1-ethylpyrrolidinylmethylamino, piperidinylamino, 1-benzylpiperidinylamino, 4-(methoxy)phenylamino, 4-(3-hydroxypropyl)phenylamino, benzylamino, benzyloxy, pyridiylmethylamino group.

It will be appreciated that where two or more R^{12} substituents are present, these need not necessarily be the same atoms and/or groups.

In general, when R^8 is a heteroaliphatic, heterocycloaliphatic or heteroaromatic group it is attached to the remainder of the molecule of formula (1) through any available heteroatom or group or, preferably, carbon atom.

The groups R^2, R^3, R^7 and additionally R^{10} and/or R^{10a} [where present] in compounds of formula (1) may each individually be an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group. In each case, the aliphatic, cycloalphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group may be as particularly described above for R^8 when it represents one of these groups.

Halogen atoms represented by the groups R^2, R^3 and/or R^6 in compounds of formula (1) include for example fluorine, chlorine, bromine or iodine atoms.

Substituted amino groups represented by the groups R^1, R^2, R^3 and/or R^6 in compounds of formula (1) include groups such as $-NHR^{15}$ [where R^{15} is an optionally substituted straight or branched C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl group], $-NR^{15}R^{16}$ [where R^{15} and R^{16} are the same or different and R^{16} is an optionally substituted alkyl, alkenyl or alkynyl group as just described for R^{15}], $-N(R^{17})COR^{15}$, [where R^{17} is a hydrogen atom or a group R^{15} as just described], $-N(R^{17})SO_2R^{18}$ [where R^{18} is as described for R^{17}] $-N[SO_2R^{18}]_2$, $-N(R^{17})SO_2NR^{17}R^{18}$, $-N(R^{17})CONR^{17}R^{18}$, or $-N(R^{17})CSNR^{17}R^{18}$. Particular examples of R^{15}, R^{16}, R^{17} and R^{18} alkyl, alkenyl or alkynyl groups include optionally substituted methyl, ethyl, n-propyl, i-propyl, allyl or ethynyl groups. Optional substituents include those described above in relation to the group R^8 when R^8 is an optionally substituted aliphatic group.

Particular examples of substituted amino groups represented by R^2, R^3 and/or R^6 include $-NHCH_3$, $-N(CH_3)_2$, $-NHCH_2CH_3$, $-N(CH_2CH_3)_2$, $-NHCOCH_3$, $-NHSO_2H$, $-NHSO_2CH_3$, $-NHSO_2NH_2$, $-NHSO_2NHCH_3$, $-NHSO_2N(CH_3)_2$, $-NHCONH_2$, $-NHCONHCH_3$ or $-NHCONHCH_2CH_3$ groups.

Optionally substituted straight or branched alkyl, alkenyl or alkynyl groups represented by R^5 and/or R^{6a} [when present] include optionally substituted C_{1-6}alkyl, C_{2-6}alkenyl or C_{2-6}alkynyl as described above for R^8 aliphatic groups.

Straight or branched alkyl groups represented by the group R^4 in compounds of the invention include straight or branched C_{1-6}alkyl groups such as methyl or ethyl groups.

The presence of certain substituents in the compounds of formula (1) may enable salts of the compounds to be formed. Suitable salts include

pharmaceutically acceptable salts, for example acid addition salts derived from inorganic or organic acids, and salts derived from inorganic and organic bases.

Acid addition salts include hydrochlorides, hydrobromides, hydroiodides, alkylsulphonates, e.g. methanesulphonates, ethanesulphonates, or isethionates, arylsulphonates, e.g. p-toluenesulphonates, besylates or napsylates, phosphates, sulphates, hydrogen sulphates, acetates, trifluoroacetates, propionates, citrates, maleates, fumarates, malonates, succinates, lactates, oxalates, tartrates and benzoates.

Salts derived from inorganic or organic bases include alkali metal salts such as sodium or potassium salts, alkaline earth metal salts such as magnesium or calcium salts, and organic amine salts such as morpholine, piperidine, dimethylamine or diethylamine salts.

Particularly useful salts of compounds according to the invention include pharmaceutically acceptable salts, especially acid addition pharmaceutically acceptable salts.

It will be appreciated that depending on the nature of the substituents R^1-R^3 and R^5 - R^7 the compounds of formula (1) may exist as geometrical isomers and/or may have one or more chiral centres so that enantiomers or diasteromers may exist. It is to be understood that the invention extends to all such isomers of the compounds of formula (1), and to mixtures thereof, including racemates.

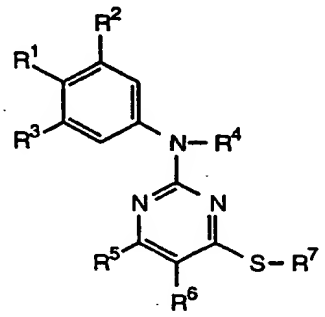
In one class of compounds of formula (1) the groups R^1, R^2, R^3, R^4, R^5, R^7 and X are as defined for formula (1), and R^6 is a hydrogen or halogen atom or a group $-X^1-R^{6a}$.

In a further preferred class of compounds of formula (1) R^4 is especially a hydrogen atom.

The groups R^5 and R^6 in compounds of formula (1) are each preferably a hydrogen atom.

R^7 in compounds of formula (1) is preferably an optionally substituted aromatic or heteroaromatic group.

A further class of compounds according to the invention has the formula 1(a):



1(a)

wherein each of R^1, R^2, R^3, R^4, R^5, R^6 and R^7 is as defined for formula (1); and the salts, solvates, hydrates and N-oxides thereof.

In these compounds, R^4 and R^5 is each preferably a hydrogen atom. R^6 is preferably a group $-X^1R^{6a}$ where X^1 is as defined for formula (1) and R^{6a} is an optionally substituted straight or branched chain alkyl group, or R^6 is especially a hydrogen atom. R^7 in compounds of formula (1a) is preferably an optionally substituted aromatic or heteroaromatic group.

The aromatic or heteroaromatic R^7 group in compounds of formulae (1) or 1(a) in general may be as defined previously for compounds of formula (1). In one preference, however, R^7 is an optionally substituted phenyl, 1- or 2-naphthyl or heteroaromatic group containing one or two oxygen, sulphur and/or nitrogen atoms. Thus in particular R^7 may be an optionally substituted phenyl, 1- or 2-naphthyl, pyrrolyl, furyl, thienyl, indolyl, pyrazolyl, thiazolyl, [2,3-dihydro]benzofuryl, benzothiazolyl, 2-pyridyl, 3-pyridyl or 4-pyridyl group. Particularly useful groups include optionally substituted phenyl, particularly 3-substituted phenyl groups, 2-pyridyl, 3-pyridyl or 4-pyridyl groups. The aromatic or heteroaromatic group may in

particular be attached to the remainder of the compound of formula (1) through any available ring carbon atom.

In general, the optional substituents which may be present on aromatic or heteroaromatic R^7 groups in compounds of formulae (1) or (1a) include one, two, or three R^{12} substituents as generally and particularly described above and hereinafter in the Examples. Particularly useful R^{12} substituents include $-NHR^{14}$, $-AlkNH_2$, $-AlkNHR^{14}$, $-OR^{14}$, $-AlkCO_2H$ or $-AlkCO_2Alk^1$ groups where R^{14}, Alk and Alk^1 are as generally and particularly defined above. Useful members of these substituents include those wherein R^{14} is an -Alk, $-AlkNH_2$ or -Alk-heterocycloalkyl group. In these, and the other preferred substituents just mentioned, Alk and Alk^1 when present is each preferably a C_{1-6}alkyl group.

In the compounds of formula (1) and (1a) R^1 is preferably an $-R^8$ or in particular an $-OR^8$ group. The group R^1 is preferably attached at the 3- or 4- position of the phenyl ring. When R^1 is at the 3- positon any R^2 and/or R^3 substituent is preferably at the 4- and/or 5- positions. When R^1 is at the 4- position any R^2 and/or R^3 substituent is preferably attached at the 3- and/or 5- positions.

Particularly useful $-R^8$ groups include heterocycloaliphatic groups of the type generally described above, especially optionally substituted C_{3-7} cycloalkyl groups containing one or two heteroatoms such as pyrrolidinyl or morpholinyl groups. Particularly useful $-OR^8$ groups include optionally substituted alkoxy groups such as optionally substituted ethoxy groups. Particularly useful substituents include amino or substituted amino groups or, especially, $-NHet^1$ groups where $-NHet^1$ is as defined above.

In these last compounds, and in general, the groups R^2 and R^3 is each preferably a methyl or methoxy group or a hydrogen atom.

Particularly useful compounds according to the invention are:
4-(3-methoxyphenylsulphanyl)-N-{[3,5-dimethyl-4-(2-(pyrrolidin-1-yl)-ethoxy]phenyl}-2-pyrimidineamine ;

4-(3-Carboxyphenylsuphanyl)-N-{[3,5-dimethyl-4-(2-pyrrolidin-1-yl)-ethoxy]phenyl}-2-pyrimidineamine;
N-[4,5-Dimethoxy-3-(2-pyrrolidin-1-ylethoxy)]-4-(3-methoxyphenyl-sulphanyl)-2-pyrimidineamine;
4-(3-Methoxyphenylsulphanyl)-N-{4-methoxy-[3-(2-pyrrolidin-1-yl)-ethoxy]phenyl}2-pyrimidineamine;
N-{3,5-Dimethoxy-4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}-4-(3-methoxy-phenylsulphanyl)-2-pyrimidineamine;
N-{[4,5-Dimethoxy-3-(2-pyrrolin-1-yl)ethoxy]phenyl}-4-(4-fluorophenyl-sulphanyl) pyrimidine-2-amine;
4-(3-Bromophenylsulphanyl)-N-[4,5-dimethoxy-3-(2-pyrrolidin-1-yl-ethoxy)phenyl]-2-pyrimidineamine;
N-{3,5-Dichloro-4-[(2-pyrrolidin-1-yl)ethoxy]phenyl}-4-(3,5-dimethyl-phenylsulphanyl)-2-pyrimidineamine;
and the salts, solvates and hydrates thereof.

Compounds according to the invention are potent and selective inhibitors of protein kinases, especially those of the src family, as demonstrated by their inhibition of enzymes such as $p56^{lck}$ and $p59^{fyn}$. The ability of the compounds to act in this way may be simply determined by employing tests such as those described in the Examples hereinafter.

The compounds according to the invention are thus of particular use in the prophylaxis and treatment of diseases in which inappropriate protein tyrosine kinase action plays a role, for example in autoimmune diseases such as rheumatoid arthritis, multiple sclerosis, and systemic lupus erythematosus, in transplant rejection, in graft v host disease, in hyperproliferative disorders such as tumours, psoriasis, in pannus formation in rheumatoid arthritis, restenosis following angioplasty and atherosclerosis, in osteoporosis and in diseases in which cells receive pro-inflammatory signals such as asthma, inflammatory bowel disease and pancreatitis.

For the prophylaxis or treatment of disease the compounds according to the invention may be administered as pharmaceutical compositions, and according to a further aspect of the invention we provide a pharmaceutical

composition which comprises a compound of formula (1) together with one or more pharmaceutically acceptable carriers, excipients or diluents.

Pharmaceutical compositions according to the invention may take a form suitable for oral, buccal, parenteral, nasal, topical or rectal administration, or a form suitable for administration by inhalation or insufflation.

For oral administration, the pharmaceutical compositions may take the form of, for example, tablets, lozenges or capsules prepared by conventional means with pharmaceutically acceptable excipients such as binding agents (e.g. pregelatinised maize starch, polyvinylpyrrolidone or hydroxypropyl methylcellulose); fillers (e.g. lactose, microcrystalline cellulose or calcium hydrogen phosphate); lubricants (e.g. magnesium stearate, talc or silica); disintegrants (e.g. potato starch or sodium glycollate); or wetting agents (e.g. sodium lauryl sulphate). The tablets may be coated by methods well known in the art. Liquid preparations for oral administration may take the form of, for example, solutions, syrups or suspensions, or they may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may be prepared by conventional means with pharmaceutically acceptable additives such as suspending agents, emulsifying agents, non-aqueous vehicles and preservatives. The preparations may also contain buffer salts, flavouring, colouring and sweetening agents as appropriate.

Preparations for oral administration may be suitably formulated to give controlled release of the active compound.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds for formula (1) may be formulated for parenteral administration by injection e.g. by bolus injection or infusion. Formulations for injection may be presented in unit dosage form, e.g. in glass ampoule or multi dose containers, e.g. glass vials. The compositions for injection may take such forms as suspensions, solutions or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as

suspending, stabilising, preserving and/or dispersing agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile pyrogen-free water, before use.

In addition to the formulations described above, the compounds of formula (1) may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation or by intramuscular injection.

For nasal administration or administration by inhalation, the compounds for use according to the present invention are conveniently delivered in the form of an aerosol spray presentation for pressurised packs or a nebuliser, with the use of suitable propellant, e.g. dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas or mixture of gases.

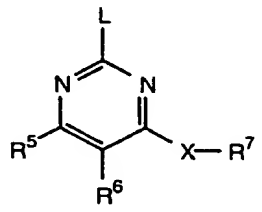
The compositions may, if desired, be presented in a pack or dispenser device which may contain one or more unit dosage forms containing the active ingredient. The pack or dispensing device may be accompanied by instructions for administration.

The quantity of a compound of the invention required for the prophylaxis or treatment of a particular condition will vary depending on the compound chosen, and the condition of the patient to be treated. In general, however, daily dosages may range from around 100ng/kg to 100mg/kg e.g. around 0.01mg/kg to 40mg/kg body weight for oral or buccal administration, from around 10ng/kg to 50mg/kg body weight for parenteral administration and around 0.05mg to around 1000mg e.g. around 0.5mg to around 1000mg for nasal administration or administration by inhalation or insufflation.

The compounds of the invention may be prepared by a number of processes as generally described below and more specifically in the Examples hereinafter. In the following process description, the symbols R^1-R^7 when used in the formulae depicted are to be understood to represent those groups described above in relation to formula (1) unless

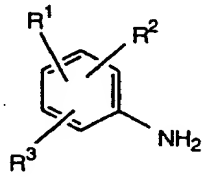
otherwise indicated. In the reactions described below, it may be necessary to protect reactive functional groups, for example hydroxy, amino, thio or carboxy groups, where these are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice [see, for example, Green, T. W. in "Protective Groups in Organic Synthesis", John Wiley and Sons, 1991]. In some instances, deprotection may be the final step in the synthesis of a compound of formula (1) and the processes according to the invention described hereinafter are to be understood to extend to such removal of protecting groups.

Thus according to one aspect of the invention, a compound of formula (1) wherein R^4 is a hydrogen atom may be prepared by displacement of a leaving atom or group in a pyrimidine of formula (2):



(2)

[where L is a leaving atom or group] with an aniline of formula (3):

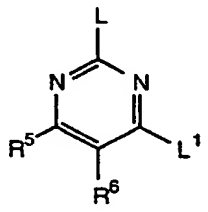


(3)

Particular leaving atoms or groups represented by L include for example halogen atoms, e.g. bromine, iodine or chlorine atoms, and sulphonyloxy groups, e.g. alkylsulphonyloxy groups, such as trifluoromethylsulphonyloxy, and arylsulphonyloxy groups, such as p-toluenesulphonyloxy.

The reaction may be performed at an elevated temperature, for example the reflux temperature, where necessary in the presence of a solvent, for example a ketone such as acetone, an alcohol such as ethanol or 2-ethoxyethanol or an aromatic hydrocarbon such as toluene, optionally in the presence of a base, for example an organic amine such as triethylamide or pyridine, or an acid, for example an inorganic acid such as hydrochloric acid.

Intermediate pyrimidines of formula (2) are either known readily available compounds or may be prepared by displacement of a leaving group from a pyrimidine of formula (4):



(4)

[where L^1 is a leaving atom or group as described above for the group L] using a thiol R^7SH. The reaction may be performed in the presence of a base such as sodium hydride in a solvent such as an amide, e.g. dimethylformamide at a low temperatue of around O°C.

The pyrimidines of formula (4) and the nucleophilic reagents R^7SH are either known compounds or may be prepared using methods analogous to those used for the preparation of the known compounds.

The anilines of formula (3) are either known compounds or may be obtained by conventional procedures, for example by hydrogenation of the corresponding nitro derivatives using for example hydrogen in the presence of a metal catalyst in a suitable solvent, for example as more particularly described in the interconversion reactions discussed below, or by use of the corresponding nitro derivative and a reducing agent such as sodium hydrosulphite in a solvent such as ethanol at an elevated temperature such as the reflux temperature. The nitrobenzenes for this

particular reaction are either known compounds or may be prepared using similar methods to those used for the preparation of the known compounds, for example by treatment of the corresponding benzene with nitric acid in the presence of an acid such as acetic acid at around ambient to the reflux temperature.

Compounds of formula (1) may also be prepared by interconversion of other compounds of formula (1) and it is to be understood that the invention extends to such interconversion processes. Thus, for example, standard substitution approaches employing for example alkylation, arylation, acylation, thioacylation, sulphonylation, formylation or coupling reactions may be used to add new substitutents to and/or extend existing substituents in compounds of formula (1). Alternatively existing substituents in compounds of formula (1) may be modified by for example oxidation, reduction or cleavage reactions to yield other compounds of formula (1).

The following describes in general terms a number of approaches which can be employed to modify existing R^1, R^2, R^3, R^4, R^5, R^6 and/or R^7 groups in compounds of formula (1). It will be appreciated that each of these reactions may only be possible where an appropriate functional group exists in a compound of formula (1). Equally, any of the following reactions may be used to generate appropriately substituted intermediates of formulae (2), (3) and (4) for use in the preparation of compounds of formula (1).

Thus, for example alkylation or arylation of a compound of formula (1) may be achieved by reaction of the compound with a reagent R^8L (where R^8 is as defined above except for a hydrogen atom) or $(R^{13})_mAlkL$ where L is as previously defined.

The alkylation or arylation reaction may be carried out in the presence of a base, e.g. an inorganic base such as a carbonate, e.g. caesium or potassium carbonate, an alkoxide, e.g. potassium t-butoxide, or a hydride, e.g. sodium hydride, in a dipolar aprotic solvent such as an amide, e.g. a

substituted amide such as dimethylformamide or an ether, e.g. a cyclic ether such as tetrahydrofuran, at around 0°C to around 40°C.

In a variation of this process the leaving group L may be alternatively part of the compound of formula (1) and the reaction performed with an appropriate nucleophilic reagent such as an amine in a solvent such as an alcohol, e.g. ethanol, or an amide such as dimethylformamide at an elevated temperature, e.g. the reflux temperature.

In another general example of an interconversion process, a compound of formula (1) may be acylated or thioacylated. The reaction may be performed for example with an acyl halide or anhydride in the presence of a base, such as a tertiary amine e.g. triethylamine in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane or carbon tetrachloride, or an alcohol, e.g. methanol at for example ambient temperature, or by reaction with a thioester in an inert solvent such as tetrahydrofuran at a low temperature such as around 0°C. The reaction is particularly suitable for use with compounds of formula (1) containing primary or secondary amino groups.

In a further general example of an interconversion process, a compound of formula (1) may be formylated, for example by reaction of the compound with a mixed anhydride $HCOOCOCH_3$ or with a mixture of formic acid and acetic anhydride.

Compounds of formula (1) may be prepared in another general interconversion reaction by sulphonylation, for example by reaction of the compound with a reagent $(R^{13})_mAlkS(O)_2L$, or $R^8S(O)_2L$ in the presence of a base, for example an inorganic base such as sodium hydride in a solvent such as an amide, e.g. a substituted amide such as dimethylformamide at for example ambient temperature. The reaction may in particular be performed with compounds of formula (1) possessing a primary or secondary amino group.

In further examples of interconversion reactions according to the invention compounds of formula (1) may be prepared from other compounds of formula (1) by modification of existing functional groups in the latter.

Thus in one example, ester groups $-CO_2Alk^1$ in compounds of formula (1) may be converted to the corresponding acid [$-CO_2H$] by acid- or base-catalysed hydrolysis or by catalytic hydrogenation depending on the nature of the group Alk^1. Acid- or base-catalysed hydrolysis may be achieved for example by treatment with an organic or inorganic acid, e.g. trifluoroacetic acid in an aqueous solvent or a mineral acid such as hydrochloric acid in a solvent such as dioxan or an alkali metal hydroxide, e.g. lithium hydroxide in an aqueous alcohol, e.g. aqueous methanol. Catalytic hydrogenation may be carried out using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as an ether, e.g. tetrahydrofuran or an alcohol, e.g. methanol. Similarly, base-catalysed hydrolysis with for example an alkali metal hydroxide such as sodium hydroxide in a solvent such as an alcohol e.g. ethanol may be used to convert a $>NSO_2Alk(R^{13})_m$ or $>NSO_2R^8$ group to a >N-H group.

In a second example, $-OAlk^2$ [where Alk^2 represents an alkyl group such as a methyl group] groups in compounds of formula (1) may be cleaved to the corresponding alcohol [-OH] by reaction with boron tribromide in a solvent such as a halogenated hydrocarbon, e.g. dichloromethane at a low temperature, e.g. around -78°C.

Alcohol [-OH] groups may also be obtained by hydrogenation of the corresponding $-OCH_2R^8$ group in which R^8 is an aromatic group using for example hydrogen in the presence of a metal catalyst, for example palladium on a support such as carbon in a solvent such as ethanol in the presence of ammonium formate. In another example, -OH groups may be generated from the corresponding ester [$-CO_2Alk$] by reduction using for example a complex metal hydride such as lithium aluminium hydride.

In a further example, alcohol -OH groups in compounds of formula (1) may be converted to a corresponding $-OAlk(R^{13})_m$ or $-OR^8$ group where R^8 is

as described for formula (1) other than a hydrogen atom by coupling with a reagent $(R^{13})_mAlkOH$ or R^8OH in a solvent such as tetrahydrofuran in the presence of a phosphine, e.g. triphenylphosphine and an activator such as diethyl-, diisopropyl-, or dimethylazodicarboxylate.

In another example of an interconversion reaction, amines of formula (1) may be alkylated using a reductive alkylation process employing an aldehyde and a borohydride, for example sodium triacetoxyborohydride, in a solvent such as dichloromethane, in the presence of an acid such as acetic acid at around ambient temperature.

In a further example, amide groups in compounds of formula (1) may be obtained by coupling an acid [$-CO_2H$] or an active derivative thereof, e.g. an acid anhydride, ester, imide or halide, with an amine in which either the acid or amine forms part of the starting material of formula (1). The coupling reaction may be performed using standard conditions for reactions of this type. Thus for example the reaction may be carried out in a solvent, for example an inert organic solvent such as an amide, e.g. a substituted amide such as dimethylformamide, at a low temperature, e.g. -30°C to ambient temperature, optionally in the presence of a base, e.g. an organic base such as a cyclic amine, e.g. N-methylmorpholine, and where necessary in the presence of a condensing agent, for example a diimide such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide advantageously in the presence of a catalyst such as a N-hydroxy compound, e.g. a N-hydroxytriazole such as hydroxyazabenzotriazole..

Urea groups in compounds of formula (1) may be prepared by reaction of a corresponding amine [$-NH_2$] with an isocyanate, e.g. ethyl isocyanate, in a solvent, e.g. dichloromethane, at ambient temperature.

Aminosulphonylamino [$-NHSO_2NH_2$] groups in compounds of formula (1) may be obtained, in another example, by reaction of a corresponding amine [$-NH_2$] with sulphamide in the presence of an organic base such as pyridine at an elevated temperature, e.g. the reflux temperature.

In a further example, amine [-NH_2] groups in compounds of formula (1) may be obtained by hydrolysis from a corresponding imide by reaction with hydrazine in a solvent such as an alcohol, e.g. ethanol at ambient temperature.

In another example, a nitro [-NO_2] group may be reduced to an amine [-NH_2], for example by catalytic hydrogenation as just described, or by chemical reduction using for example a metal, e.g. tin or iron, optionally in the presence of an acid such as hydrochloric acid and a solvent such as an alcohol, e.g. methanol or ethanol.

In a further example of an interconversion process, a tetrazole substituent may be obtained from the corresponding nitrile by treatment of the latter with an azide, e.g. sodium azide, in a solvent such as a substituted amine, e.g. dimethylformamide at an elevated temperature.

N-oxides of compounds of formula (1) may be prepared for example by oxidation of the corresponding nitrogen base using an oxidising agent such as hydrogen peroxide in the presence of an acid such as acetic acid, at an elevated temperature, for example around 70°C to 80°C, or alternatively by reaction with a peracid such as peracetic acid or 3-chloroperoxybenzoic acid in a solvent, e.g. dichloromethane, at ambient temperature.

Where salts of compounds of formula (1) are desired, these may be prepared by conventional means, for example by reaction of a compound of formula (1) with an appropriate acid or base in a suitable solvent or mixture of solvents, e.g. an organic solvent such as an ether, e.g. diethylether, or an alcohol, e.g. ethanol.

The following Examples illustrate the invention. In the Examples all ^{1}Hnmr were run at 300MHz unless specified otherwise. All temperatures are in °C. The following abbreviations are used: DMSO - dimethylsulphoxide; DMF - dimethylformamide. In many of the following Examples 2-chloro-4-(3-methoxyphenylsulphanyl)pyrimidine is used as a starting material.

The preparation of this compound is described in Example 1. Where it is used in other Examples it is referred to as Intermediate A.

EXAMPLE 1

4-(3-Methoxyphenylsulphanyl)-N-[3,5-dimethyl-4-(2-pyrrolidin-1-yl)-ethoxy]phenyl}-2-pyrimidineamine dihydrochloride

A mixture of 2-chloro-4-(3-methoxyphenylsulphanyl)pyrimidine (140mg, 0.55mmol) and 3,5-dimethyl-4-(2-(1-pyrrolidino)ethoxy)aniline (130mg, 0.55mmol) was heated at reflux under a nitrogen atmosphere in ethoxyethanol (4ml) containing 1M hydrochloric acid in diethyl ether (0.55ml), for 2h. After this time the solvent was removed under reduced pressure, the residue partitioned between CH_2Cl_2 and saturated aqueous $NaHCO_3$ solution, and the organic phase was dried ($MgSO_4$) and concentrated. The residue was subjected to column chromatography (silica, 5% methanol-CH_2Cl_2) and the product dissolved in ethyl acetate (5ml) and treated with 1M hydrochloric acid in diethyl ether. The resulting precipitate was collected and dried to give the title compound (100mg) as a yellow solid m.p. 94-96°. δ_H (d^6 DMSO) 11.21 (1H, br s), 9.73 (1H, br s), 8.17 (1H, d, J 5.6Hz), 7.46-7.41 (1H, m), 7.23 (2H, s), 7.21-7.18 (2H, m), 7.13-7.10 (1H, m), 6.34 (1H, d, J 5.2Hz), 4.34 (1H, br s), 4.10-4.04 (2H, m), 3.75 (3H, s), 3.65-3.53 (4H, m), 3.20-3.11 (2H, m), 2.16 (6H, s) and 2.02-1.94 (4H, m).

The 2-chloro-4-(3-methoxyphenylsulphanyl)pyrimidine used as starting material was prepared by adding a solution of 3-methoxybenzenethiol (0.84ml, 6.71mmol) in dry DMF (30ml) to a suspension of sodium hydride [60% dispersion in oil] (295mg, 7.40mmol) in DMF (30ml) at 0°, and stirring for 10min before addition of 2,4-dichloropyrimidine (1.0g, 6.71mmol). After continued stirring at 0° for 2h, the solvent was removed under reduced pressure and the residue partitioned between ethyl acetate (100ml) and 1M aqueous NaOH (75ml). The organic layer was dried, concentrated under reduced pressure and the residue subjected to column chromatography. The resulting oil was taken up in diethyl ether-hexane to give the desired product (1.08g) as a white solid, m.p. 65-66°. δ_H ($CDCl_3$) 8.18 (1H, d, J 5.4Hz), 7.41 (1H, t, J 8.09Hz), 7.20-7.05 (3H, m), 6.65 (1H, d, J 5.4Hz) and 3.85 (3H, s).

The compounds of Examples 2 and 3 were prepared in a similar manner:

EXAMPLE 2

N-(4-(2-Dimethylaminoethoxy)phenyl)-4-(4-methoxyphenyl-sulphanyl)-2-pyrimidineamine

from 4-(2-dimethylaminoethoxy)aniline (180mg, 1.0mmol), 2-chloro-4-(4-methoxyphenylsulphanyl)pyrimidine (253mg, 1.0mmol) and 1M hydrochloric acid in diethyl ether (1.0ml, 1.0mmol) to give the title compound (160mg) as a white solid m.p. 112-113°. δH ($CDCl_3$) 7.99 (1H, d, J 5.4Hz), 7.51 (2H, d, J 8.7Hz), 7.27 (2H, d, J 9.0Hz), 6.99-6.96 (3H, m), 6.78 (2H, d, J 9.0JHz), 6.23 (1H, d, J 5.4Hz), 4.04 (2H, t, J 5.7Hz), 3.87 (3H, s), 2.73 (2H, t, J 5.7Hz) and 2,34 (6H, s).

The 2-chloro-4-(4-methoxyphenylsulphanyl)pyrimidine was prepared in a similar manner to the analogous starting material of Example 1, from 4-methoxybenzenethiol (1.90g, 13.4mmol), 2,4-dichloropyrimidine (2.0g, 13.4mmol) and sodium hydride [60% dispersion in oil] (590mg, 14.8mmol) as an off-white solid m.p. 69-70°.

EXAMPLE 3

4-(3-Methoxyphenylsulphanyl)-N-[3-(4-methylpiperazinyl)phenyl]-2-pyrimidneamine

From Intermediate A (436mg, 1.72mmol), 3-(4-methylpiperazin-1-yl)aniline (330mg, 1.72mmol) and 1M hydrogen chloride in diethyl ether (1.72ml) to give the title compound (70mg) as a yellow solid m.p. 105-106°. δH ($CDCl_3$) 8.04 (1H, d, J 5.4Hz), 7.04-6.95 (2H, m), 6.59 (1H, dd, J 8.0, 1.8Hz), 6.26 (1H, d, J 5.4Hz), 3.81 (3H, s), 3.23-3.19 (4H, m), 2.58-2.54 (4H, m) and 2.34 (3H, s).

EXAMPLE 4

N-(4-Hydroxyphenyl)-4-(4-methylphenylsulphanyl)-2-pyrimidineamine

A mixture of 2-chloro-4-(4-methylphenylsulphanyl)pyrimidine (100mg, 0.42 mmol) and 4-aminophenol (55mg, 0.5mmol) was heated at reflux in ethoxyethanol (2ml) for 1.5h. The reaction was concentrated under reduced pressure and subjected to column chromatography [silica, 20% ethyl acetate-CH_2Cl_2] to give the title compound (60mg) as a buff solid m.p. 179-180°. δH ($CDCl_3$) 8.01 (1H, d, J 5.4Hz), 7.50-7.45 (2H, m),

7.31-7.27 (4H, m), 6.93 (1H, br s), 6.71-6.66 (2H, m), 6.25 (1H, d, J 5.4Hz), 4.70 (1H, br s) and 2.44 (3H, s).

The 2-chloro-4-(4-methylphenylsulphanyl)pyrimidine was prepared in a similar manner to the analogous starting material of Example 1, from p-thiocresol (838mg, 6.71mmol), 2,4-dichloropyrimidine (1.0g, 6.71mmol) and sodium hydride [60% dispersion in oil] (295mg, 7.4mmol), m.p. 80-81°. δH ($CDCl_3$) 8.15 (1H, d, J 5.4Hz), 7.46 (2H, d, J 8.0Hz), 7.30 (2H, d, J 8.0Hz), 6.59 (1H, d, J 5.4Hz) and 2.43 (3H, s).

The compounds of Examples 5 - 17 were prepared in a similar manner to the compound of Example 4:

EXAMPLE 5

N-(4-Benzyloxyphenyl)-4-(4-methoxyphenylsulphanyl)-2-pyrimidine

from 2-chloro-4-(4-methoxyphenylsulphanyl)pyrimidine (7.51g, 6.0mmol - see Example 2) and 4-benzyloxyaniline (2.83g, 12.9mmol) to give the title compound (1.60g) as a white solid m.p. 146-147°. δH ($CDCl_3$) 8.00 (1H, d, J 5.4Hz), 7.53 (2H, d, J 8.8Hz), 7.45-7.27 (7H, m), 7.02-6.96 (3H, m), 6.85 (2H, d, J 9.0Hz), 6.24 (1H, d, J 5.4Hz), 5.04 (2H, s) and 3.88 (3H, s).

EXAMPLE 6

4-(3-Methoxyphenylsulphanyl)-N-(4-morpholinophenyl)-2-pyrimidine-amine

from Intermediate A (300mg, 1.19 mmol) and 4-morpholinoaniline (211mg, 1.19mmol) to give the title compound as an off-white solid m.p. 159-161°. δH ($CDCl_3$) 8.01 (1H, dd, J 5.3, 2.7Hz), 7.40-7.37 (3H, m), 7.33 (1H, dd, J 6.5, 2.1Hz), 7.30 (1H, br s), 7.05-7.01 (1H, m), 6.96 (1H, s), 6.80 (2H, d, J 8.9Hz), 6.27 (1H, dd, J 5.3, 2.7Hz), 3.88-3.83 (4H, m), 3.80 (3H, s), 3.11-3.08 (4H, m).

EXAMPLE 7

N-(3-Hydroxyphenyl)-4-(3-methoxyphenylsulphanyl)-2-pyrimidineamine hydrochloride

From Intermediate A (1.0g, 3.96mmol) and 3-aminophenol (437mg, 4.0mmol) to give the title compound (930mg) as a white solid m.p. 144-145°. δH ($CDCl_3$) 8.06 (1H, d, J 5.4Hz), 7.39 (1H, t, J 7.9Hz), 7.26-7.03

(5H, m), 6.71 (1H, dd, J 7.9, 1.6Hz), 6.46 (1H, dd, J 7.9, 2.4Hz), 6.42 (1H, d, J 5.4Hz), 5.57 (1H, br s) and 3.82 (3H, s).

EXAMPLE 8

N-(4-Carboxyphenyl)-4-(3-methoxyphenylsulphanyl)pyrimidine-2-amine hydrochloride

From Intermediate A (500mg, 1.98mmol) and 4-aminobenzoic acid (274mg, 2.0mmol) to give the title compound (350mg) as a yellow solid m.p. 242-243°. δH (d^6 DMSO) 10.21 (1H, br s), 8.25 (1H, d, J 5.5Hz), 7.69 (2H, d, J 8.8Hz), 7.56 (2H, d, J 8.8Hz), 7.48 (1H, t, J 8.1Hz), 7.23-7.16 (3H, m), 6.62 (1H, d, J 5.5Hz) and 3.78 (3H, s).

EXAMPLE 9

N-(3-Hydroxy-4-methoxy)phenyl-4-(3-methoxyphenylsulphanyl)-2-pyrimidineamine

From Intermediate A (4.55g, 18mmol) and 5-amino-2-methoxyphenol (2.51g, 18mmol) to give the title compound as a yellow solid m.p. 182-183°. δH ($CDCl_3$) 10.40 (1H, br s), 7.77 (1H, d, J 6.6Hz), 7.45-7.39 (1H, m), 7.15 (1H, d, J 7.8Hz), 7.10-7.07 (2H, m), 6.99 (1H, d, J 2.5Hz), 6.78 (1H, dd, J 8.7, 2.5Hz), 6.65 (1H, d, J 8.7Hz), 6.47 (1H, d, J 6.6Hz), 5.63 (1H, br s), 3.87 (3H, s) and 3.78 (3H, s).

EXAMPLE 10

N-[3-(2-Hydroxyethyl)phenyl]-4-(3-methoxyphenylsulphanyl)-2-pyrimidineamine

From Intermediate A (1.07g, 4.2mmol) and 3-aminophenethyl alcohol (576mg, 4.2mmol) to give the title compund (1.1g) as a yellow solid m.p. 122-124°. δH ($CDCl_3$) 8.05 (1H, d, J 5.4Hz), 7.40-7.30 (3H, m), 7.22-7.13 (4H, m), 7.03 (1H, ddd, J 8.3, 2.6, 1.0Hz), 6.86 (1H, d, J 7.6Hz), 6.32 (1H, d, J 5.4Hz), 3.86-3.81 (5H, m) and 2.81 (2H, t, J 6.5Hz).

EXAMPLE 11

N-[3-Hydroxy-5-(1,1,1-trifluoromethyl)phenyl]-4-(3-methoxyphenyl-sulphanyl)-2-pyrimidineamine hydrochloride

From Intermediate A (2.0g, 7.9mmol) and 3-amino-5-(1,1,1-trifluoromethyl)phenyl (1.4g, 7.9mmol) to give the title compound (2.0g) as

a white solid m.p. 163-164°. δH (d^6 DMSO) 9.98 (1H, br s), 8.22 (1H, d, J 5.4Hz), 7.56 (1H, s), 7.48-7.43 (2H, m), 7.24-7.21 (2H, m), 7.15-7.12 (1H, m), 6.66 (1H, s), 6.24 (1H, d, J 5.4Hz) and 3.79 (3H, s).

EXAMPLE 12

N-(3-Hydroxymethyl)phenyl-4-(3-methoxyphenylsulphanyl)-2-pyrimidineamine hdyrochloride

From Intermediate A (3.79g, 15mmol) and 3-aminobenzyl alcohol (1.85g, 15mmol) to give the title compound (3.14g) as a yellow solid m.p. 124-125°. δH (d^6 DMSO) 10.18 (1H, br s), 8.22 (1H, d, J 5.7Hz), 7.88 (1H, br s), 7.49-7.36 (4H, m), 7.22-7.14 (3H, m), 7.07 (1H, t, J 7.7Hz), 6.93 (1H, d, J 7.6Hz), 6.52 (1H, d, J 5.7Hz), 4.41 (2H, s) and 3.77 (3H, s).

EXAMPLE 13

N-(3-Aminomethylphenyl)-4-(3-methoxyphenylsulphanyl)-2-pyrimidineamine

From Intermediate A (2.53g, 10mmol) and 3-aminobenzylamine hydrochloride (1.59g, 10mmol) to give the title compound (1.5g) as a yellow solid m.p. 120-121°. δH (d^6 DMSO) 10.11 (1H, br s), 8.54 (3H, br s), 8.23 (1H, d, J 5.6Hz), 7.52-7.44 (3H, m), 7.22-7.15 (5H, m), 6.50 (1H, d, J 5.6Hz), 3.88-3.86 (2H, br m) and 3.77 (3H, s).

EXAMPLE 14

N-(3-Chloro-4-hydroxy-5-methyl)-4-(3-methoxyphenyl-sulphanyl)pyrimidine

From Intermediate A (0.5g, 1.98mmol) and 4-amino-2-chloro-6-methylphenol (312mg, 1.98mmol) to give the title compound (247m) as a yellow solid m.p. 161°. δH (d^6 DMSO) 9.87 (1H, br s), 8.13 (1H, d, J 5.3Hz), 7.48 (1H, s), 7.38 (2H, m), 7.21-7.16 (3H, m), 7.11 (1H, m), 6.31 (1H, d, J 5.3Hz), 3.72 (3H, s) and 2.13 (3H, s).

EXAMPLE 15

4-(3-Bromophenylsulphanyl)-N-(3-nitrophenyl)-2-pyrimidineamine

From 4-(3-bromophenylsulphanyl)-2-chloropyrimidine (3.0g, 9.95mmol) and 3-nitroaniline (1.38g, 9.95mmol) to give the title compound (3.2g) as a yellow solid m.p. 208-209°. δH (d^6 DMSO) 10.23 (1H, s), 8.51 (1H, s),

8.28 (1H, d, J 5.4Hz), 7.89-7.69 (5H,m), 7.47 (1H, t, J 7.5Hz), 7.39 (1H, t, J 7.4Hz) and 6.58 (1H, d, J 5.4Hz).

The chloropyrimidine starting material was prepared in a similar manner to Intermediate A as a colourless solid m.p. 60-61°. δH ($CDCl_3$) 8.23 (1H, d, J 5.4Hz), 7.76 (1H, t, J 1.8Hz), 7.65 (1H, ddd, J 7.9, 1.8, 1.1Hz), 7.56-7.52 (1H, m), 7.37 (1H, t, J 7.8Hz) and 6.70 (1H, d, J 5.4Hz).

EXAMPLE 16

N-[3-(2-Hydroxyethoxy)phenyl]-4-(3-nitrophenylsulphanyl)-2-pyrimidineamine

From 2-chloro(3-nitrophenylsulphanyl)pyrimidine (1.0g, 3.75mmol prepared from 2,4-dichloropyrimidine and 3-nitrobenzenethiol according to the method of Example 1) and 3-aminophenethyl alcohol (514mg 3.75mmol) to give the title compound (350mg) as a yellow powder m.p. 160-161. δH ($CDCl_3$) 8.46 (1H, t, J 1.9Hz), 8.34-8.30 (1H, m), 8.11 (1H, d, J 5.3Hz), 7.93-7.89 (1H, m), 7.62 (1H, t, J 8.0Hz), 7.20-7.12 (3H, m), 7.03 (1H, t, J 7.8Hz), 6.84 (1H, d, J 7.5Hz), 6.48 (1H, d, J 5.3Hz), 3.81 (2H, t, J 6.4Hz) and 2.76 (1H, t, J 5.6Hz).

EXAMPLE 17

4-(3-Carboxyphenylsuphanyl)-N-{[3,5-dimethyl-4-(2-pyrrolidin-1-yl)ethoxy]phenyl}-2-pyrimidineamine sodium salt

From 4-(3-tert-butyoxycarbonylphenylsulphanyl)-2-chloropyrimidine (300mg, 0.93mmol) and 3,5-dimethyl-4-(2-pyrrolidinyl-1-yl)ethoxyaniline (234mg, 1.0mmol) to give the title compound (175mg) as an off white solid m.p. 155-156°. δH (d^6 DMSO) 8.96 (1H, s), 8.14 (1H, d, J 5.2Hz), 8.10-8.04 (2H, m), 7.79 (1H, d, J 7.9Hz), 7.58 (1H, t, J 7.8Hz), 7.17 (2H, s), 6.37 (1H, d, J 5.2Hz), 4.74 (4H, br s), 3.82 (2H, t, J 6.1Hz), 2.86 (3H, t, J 6.2Hz), 2.64-2.62 (4H, br m), 2.13 (6H, s) and 1.74-1.72 (4H, br m).

The sodium salt was formed as a result of partitioning the crude reaction residue between saturated aqueous $NaHCO_3$ and chloroform. The salt was extracted into the organic phase.

The chloropyrimidine starting material was prepared by treating a solution of 4-(3-carboxyphenylsulphanyl)-2-chloropyrimidine (500mg, 1.87mmol) in CH_2Cl_2 (25ml) with concentrated H_2SO_4 (5 drops), cooling to -78° and condensing isobutylene gas (approximately 10g) into the reaction vessel.

After condensation was complete, the cold bath was removed and the solution left at room temperature for 4h. The reaction was washed with 2M NaOH, dried ($MgSO_4$) and evaporated to give the desired material (300mg) as a colourless gum which was used for the above process without purification.

4-(3-Carboxyphenylsulphanyl)-2-chloropyrimidine was prepared by heating a solution of 2,4-dichloropyrimidine (2.97g, 19.9mmol) and 3-mercaptobenzoic acid (3.07g, 19.9mmol) in ethanol (50ml) at reflux for 1h. On cooling to 0°, the resulting precipitate was collected and dried to give the desired material (3.38g) as a white solid.

EXAMPLE 18

N [3-(2-Diethylaminoethoxy)phenyl]-4-(3-methoxyphenylsulphanyl)-2-pyrimidineamine

To a solution of the compound of Example 7 (325mg, 1.0mmol) in DMF (15ml) was added 2-diethylaminoethyl chloride hydrochloride (189mg, 1.1mmol) and caesium carbonate (717mg, 2.2mmol) and the resulting mixture heated at 100° for 4h. After this time the solvent was removed under reduced pressure to give a residue which was partitioned between CH_2Cl_2 (10ml) and brine (2 x 100ml). The organic phase was dried ($MgSO_4$) and evaporated under reduced pressure to give a residue which was subjected to column chromatography (silica; 5% methanol in CH_2Cl_2) to give a colourless gum. This was taken up in ethyl acetate (25ml) into which dry HCl gas was bubbled, and the resulting precipitate was collected and dried to give the title compound (113mg) as a yellow powder, m.p. 192-193°. δH (d^6 DMSO) 10.72 (1H, br s), 9.84 (1H, br s), 8.19 (1H, d, J 5.4Hz), 7.47 (1H, t, J 8.2Hz), 7.31-7.06 (7H, m), 6.59 (1H, d, J 8.0Hz), 6.37 (1H, d, J 5.4Hz), 4.35-4.32 (2H, m), 3.78 (3H, s), 3.48-3.46 (2H, m), 3.19-3.16 (4H, m) and 1.25 (6H, t, J 7.2Hz).

The compounds of Examples 19 and 20 were prepared in a similar manner using potassium carbonate in place of caesium carbonate.

EXAMPLE 19

N-[4,5-Dimethoxy-3-(2-pyrrolidin-1-ylethoxy)]-4-(3-methoxyphenyl-sulphanyl)-2-pyrimidineamine

From N-(3,4-dimethoxy-5-hydroxyphenyl)-4-(3-methoxyphenylsulphanyl)-2-pyrimidineamine (500mg, 1.3mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (276mg, 1.6mmol) and potassium carbonate (591mg, 4.2mmol) to give the title compound (430mg) as a yellow solid m.p. 120-121°. δH (d^6 DMSO) 11.27 (1H, br s), 9.68 (1H, s), 8.18 (1H, d, J 5.4Hz), 7.46 (1H, t, J 8.2Hz), 7.23-7.18 (3H, m), 7.13 (1H, d, J 2.4Hz), 7.11 (1H, d, J 2.4Hz), 6.21 (1H, d, J 5.4Hz), 4.31-4.27 (2H, m), 3.78 (3H, s), 3.72 (3H, s), 3.67 (3H, s), 3.63-3.56 (4H, m), 3.18-3.10 (2H, m), 2.08-2.01 (2H, m) and 1.98-1.90 (2H, m).

The pyrimidineamine starting material was prepared from Intermediate A (3.03g, 12mmol) and 5-amino-2,3-dimethoxyphenol (2.0g, 11.8mmol) in a similar procedure to Example 1 to give the desired product (1.0g) as an off-white solid m.p. 153-154°.

5-Amino-2,3-dimethoxyphenol was prepared by hydrogenation of a solution of 1-benzyloxy-2,3-dimethoxy-5-nitrobenzene (2.5g, 8.2mmol) in ethanol (45ml) over 10% palladium on charcoal (20mg) at 20psi and room temperature for 6h. The catalyst was removed by filtration through a pad of Celite® washing thoroughly with methanol. The combined filtrate and washings were evaporated to give the desired product (1.3g) as a dark grey solid.

1-Benzyloxy-2,3-diemthoxy-5-nitrobenzene was prepared by the method described in International Patent Specification No. WO97/19065.

EXAMPLE 20

4-(3-Methoxyphenylsulphanyl)-N-{4-methoxy-[3-(2-pyrrolidin-1-yl)ethoxy]phenyl}2-pyrimidineamine

From the compound of Example 9 (502mg, 1.28mmol), 1-(2-chloroethyl)pyrrolidine hydrochloride (262mg, 1.54mmol) and potassium carbonate (575mg, 4.1mmol) to give the title compound (135mg) as a buff solid m.p. 147-149°. δH (d^6 DMSO) 10.98 (1H, br s), 9.58 (1H, br s), 8.15 (1H, d, J 5.5Hz), 7.45 (1H, m), 7.30 (1H, m), 7.18-7.16 (5H, m), 6.82 (1H, br s), 6.30 (1H, d, J 5.5Hz), 4.25 (2H, br s), 3.77 (3H, s), 3.74 (3H, s), 3.56 (4H, br m) 3.12 (2H, m) and 2.00-1.82 (4H, m).

EXAMPLE 21

N-{3,5-Dimethoxy-4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}-4-(3-methoxyphenylsulphanyl)-2-pyrimidineamine dihydrochloride

To a solution of N-{3,5-dimethoxy-4-[2-(*p*-toluenesulphonyloxy)ethoxy]-phenyl}-4-(3-methoxyphenylsulphanyl)-2-pyrimidineamine (1.0g, 1.76mmol) in DMF (6ml) was added pyrrolidine (2.9ml) and the reaction heated at 70° for 2h. After this time the solvent was removed under reduced presure and the residue partioned between ethyl acetate (100ml) and saturated aqueous Na_2CO_3 (10ml). The organic phase was dried ($MgSO_4$), concentrated under reduced pressure and the residue subjected to column chromatography (silica gel; 12% methanol-CH_2Cl_2). The resulting material was taken up in ethyl acetate and treated with hydrogen chloride gas to give a precipitate which was collected by filtration and dried to give the title compund (440mg) as a yellow solid. δH (d^6 DMSO) 10.67 (1H, br s), 9.72 (1H, s), 8.19 (1H, d, J 5.5Hz), 7.45 (1H, t, J 8.1Hz), 7.22 (2H, m), 7.16-7.11 (3H, m), 6.23 (1H, d, J 5.5Hz), 4.12-4.08 (2H, m), 3.77 (3H, s), 3.73 (6H,s), 3.69-3.62 (2H, m), 3.47-3.42 (2H, m), 3.20-3.10 (2H, m) and 2.05-1.93 (4H, m).

The tosylate used as starting material was prepared by treating a solution of N-[3,5-dimethoxy-4-(2-hydroxyethoxy)phenyl]-4-(3-methoxyphenylsulphanyl)-2-pyrimidineamine (2.0g, 4.3mmol) in pyridine (6ml) with *p*-toluenesulphonyl chloride (3.28g, 17.2mmol) at room temperature for 2h. Water (25ml) was added to the reaction followed by acidification with 2M hydrochloric acid, and this was extracted with ethyl acetate (100ml). The organic phase was washed with 2M hydrochloric acid (100ml) and saturated aqueous Na_2CO_3 (100ml), dried ($MgSO_4$) and concentrated under reduced pressure to give the desired product as a light brown oil (2.31g). δH ($CDCl_3$) 8.04 (1H, d, J 5.4Hz), 7.80 (2H, d, J 8.3Hz), 7.39-7.30 (3H, s), 7.20-7.13 (2H, m), 7.03-6.99 (2H, m), 6.86 (2H, s), 6.22 (1H, d, J 5.4Hz), 4.31 (2H, t, J 5.6Hz), 4.13 (2H, t, J 5.6Hz), 3.81 (3H, s), 3.77 (6H, s) and 2.43 (3H, s).

The hydroxyethoxy starting material was prepared from Intermediate A (2.27g, 9.0mmol) and 4-(2-hydroxyethoxy)-3,5-dimethoxyaniline (1.92g,

9.0mmol) using a similar method to the compound of Example 4 to give the title compound as a yellow solid (2.4g) m.p. 173-179°.

EXAMPLE 22

4-(3-Methoxyphenylsulphanyl)-N-{4-[N'-(2-pyrrolidin-1-yl)ethyl-carboxamido]phenyl}-2-pyrimidineamine

To a solution of the compound of Example 8 (1.0g, 2.56mmol) in dry DMF (10ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (541mg, 2.82mmol), hydroxyazabenzotriazole (383mg, 2.82mmol) and N-methyl-morpholine (1.24ml, 11.29mmol) followed by 1-(2-aminoethyl)pyrrolidine (0.36ml, 2.8.2mmol) and the reaction stirred at room temperature for 4h. After this time the reaction was concentrated under reduced pressure to give a yellow oil which was partitioned between brine (250ml) and CH_2Cl_2 (250ml). The organic phase was dried ($MgSO_4$) and evaporated to a sticky white solid which was taken up in hot ethyl acetate. The resulting solution was cooled, diluted carefully with hexane and the resulting precipitate collected and dried to give the title compound (620mg) as a white solid m.p. 146-147°. δH (d^6 DMSO) 9.92 (1H, br s), 8.39 (1H, br s), 8.23 (1H, d, J 5.3Hz), 7.70-7.67 (2H, m), 7.60-7.57 (2H, m), 7.49 (1H, t, J 7.2Hz), 7.24 (3H, m), 6.48 (1H, d, J 5.3Hz), 3.79 (3H, s), 3.48 (2H, m), 2.90-2.81 (6H, m) and 1.83-1.76 (4H, m).

EXAMPLE 23

4-(3-Methoxyphenylsulphanyl)-N-[3-(2-pyrrolidin-1-yl)ethyl]-2-pyrimidineamine dihydrochloride

From 4-(3-methoxyphenylsulphanyl)-N-[3-(2-*p*-toluenesulphonyloxyethyl)-phenyl]-2-pyrimidineamine (110g) and pyrrolidine (5.1ml, 62mmol) in a manner analogous to the preparation of the compound of Example 21, to give the title compound (450mg) as a yellow solid m.p. 136-137°.

The tosylate starting material was prepared in a similar manner to the analogous intermediate of Example 21, from the compound of Example 10 (1.10g, 3.1mmol) and *p*-toluenesulphonyl chloride (2.36g, 12.4mmol) to give the desired compound (1.10g) as a yellow oil which was used without purification.

EXAMPLE 24

N-{3-[2-(Pyrrolidin-1-yl)ethoxy]phenyl}-4-(3-methoxyphenyl-sulphanyl)-2-pyrimidineamine dihydrochloride

From the compound of Example 11 (1.0g, 2.3mmol), 1-(2-chloroethyl) pyrrolidine hydrochloride (476mg, 2.8mmol) and potassium carbonate (780mg, 5.6mmol) using the method of Example 18 to give the title compound (320mg) as an off-white solid m.p. 199-200°. δH (d^6 DMSO) 11.04 (1H, br s),10.08 (1H, s), 8.25 (1H, d, J 5.4Hz), 7.78 (1H, s), 7.71 (1H, s), 7.47 (1H, t, J 8.2Hz), 7.24-7.21 (2H,m), 7.16-7.13 (1H, m), 6.90 (1H, s), 6.28 (1H, d, J 5.5Hz), 4.82 (1H, br s), 4.40 (2H, m), 3.78 (3H, s), 3.60-3.55 (4H, m), 3.14-3.08 (2H, br m) and 2.08-1.90 (4H, br m).

EXAMPLE 25

4-(3-Methoxyphenylsulphanyl)-N-(3-pyrrolidin-1-ylmethyl)phenyl pyrimidine-2-amine dihydrochloride

To a suspension of the compound of Example 12 (465mg, 1.24mmol) in $CHCl_3$ (40ml) was added thionyl chloride (0.3ml, 1.36mmol) and the resulting mixture heated at 55° for 6h. The reaction was then diluted with CH_2Cl_2 (60ml), washed with saturated aqueous $NaHCO_3$, dried ($MgSO_4$) and concentrated *in vacuo* to a yellow oil. This residue was dissolved in acetonitrile (25ml), pyrrolidine (0.52ml, 6.2mmol) added and the solution heated at reflux for 0.5h. The reaction was concentrated *in vacuo* and the residue was subjected to column chromatography (silica gel; 10% methanol in CH_2Cl_2). The resulting material was dissolved in an ethyl acetate/ethanol (1:10 v/v) mixture (10ml) and treated with 1M hydrogen chloride in diethyl ether (2ml). The precipitate which formed was collected and dried to give the title compound (300mg) as a yellow solid m.p. 115-116°. δH (d^6 DMSO) 11.17 (1H, br s), 9.96 (1H, s), 8.21 (1H, d, J 5.4Hz), 7.63-7.44 (3H, m), 7.29-7.15 (7H, m), 6.43 (1H, d, J 5.4Hz), 4.21 (2H, d, J 5.6Hz), 3.78 (3H, s0< 3.90-3.80 (2H, br m), 3.05-2.94 (2H, br m) and 2.00-1.88 (4H, br m).

EXAMPLE 26

N-(3-Aminophenyl)-4-(3-bromophenylsulphanyl)-2-pyrimidineamine

The compound of Example 15 (3.0g, 6.82mmol) was dissolved in ethanol (50ml) and tin (II) chloride dihydrate (4.62g, 20.47mmol) added. The reaction was heated at reflux for 3h, after which time 2M aqueous NaOH

(100ml) was added and the resulting suspension extracted with ethyl acetate (200ml). The organic phase was dried ($MgSO_4$) and evaporated to give the title compound (2.1g) as a pale orange solid m.p. 109-110°. δH ($CDCl_3$) 8.07 (1H, d, J 5.3Hz), 7.79 (1H, s), 7.61 (1H, d, J 8.0Hz), 7.55 (1H, d, J 7.7Hz), 7.33 (1H, t, J 7.9Hz), 7.08 (1H, br s), 6.98 (1H, t, J 8.0Hz), 6.87 (1H, s), 6.68 (1H, d, J 7.0Hz), 6.37-6.31 (2H, m) and 3.59 (2H, br s).

EXAMPLE 27

N-{[4,5-Dimethoxy-3-(2-pyrrolin-1-yl)ethoxy]phenyl}-4-(4-fluoro-phenylsulphanyl) pyrimidine-2-amine dihydrochloride

In a manner analogous to the preparation of the compound of Example 21 from N-{4,5-dimethoxy-3-(2-*p*-toluenesulphonyloxy)ethoxy]phenyl}-4-(4-fluorophenyl-sulphanyl)pyrimidine-2-amine (1.3g) and pyrrolidine (5.2ml, 62mmol) to give the title compound (550mg) as a yellow solid. δH (d^6 DMSO) 9.57 (1H, s), 8.18 (1H, d, J 5.4Hz), 7.71 (2H, dd, J 8.8, 5.4Hz), 7.39 (2H, t, J 8.8Hz), 7.15 (2H, dd, J 18.6, 2.3Hz), 6.17 (1H, d, J 5.4Hz), 4.29 (2H, m), 3.75 (2H,m), 3.72 (3H, s), 3.66 (3H, s), 3.59 (4H, m), 3.14 (2H, m), 1.98 (2H, m) and 1.89 (2H, m).

The tosylate used as starting material was prepared in a similar manner to the analogous intermediate of Example 21 from N-[4,5-dimethoxy-3-(2-hydroxyethoxy)phenyl]-4-(4-fluorophenylsulphanyl)pyrimidine-2-amine (1.3g, 3.12mmol) and *p*-toluenesulphonyl chloride (1.78g, 9.35mmol) to give the desired compound as a light yellow oil which was used without purification.

N-[4,5-Dimethoxy-3-(2-hydroxyethoxy)phenyl]-4-(4-fluorophenylsulphanyl)-pyrimidine-2-amine was prepared by treating a solution of N-(4,5-dimethoxy-3-hydroxyphenyl)-4-(4-fluorophenylsulphanyl)-2-pyrimidine-amine (2.23g, 6.0mmol) and ethyl carbonate (0.79g, 9.0mmol) in dry DMF (25ml) with potassium carbonate (1.66h, 12.0mmol) and heating the resulting mixture at 100° for 16h. The reaction was concentrated under reduced pressure and the residue partitioned between ethly acetate and water. The aqueous layer was re-extracted with ethyl acetate, the combined organic layers dried ($MgSO_4$) and evaporated to give a residue which was subjected to column chromatography [silica; 20% hexane-ethyl acetate] to give the desired compound (1.36g) as a white foam. δH (d^6

DMSO) 9.48 (1H, s), 8.17 (1H, d, J 5.3Hz), 7.69 (2H, m), 7.36 (2H, t, J 8.8Hz), 7.08 (2H, m), 6.15 (1H, d, J 5.3Hz), 4.81 (1H, t, J 5.2Hz), 3.92 (2H, t, J 5.2Hz), 3.73 (2H, m), 3.71 (3H, s) and 3.64 (3H, s).

EXAMPLE 28

4-(3-Bromophenylsulphanyl)-N-[4,5-dimethoxy-3-(2-pyrrolidin-1-ylethoxy)phenyl]-2-pyrimidineamine dihydrochloride

In a manner analogous to the preparation of the compound of Example 21 from 4-(3-bromophenylsulphanyl)-N-[4,5-dimethoxy-3-(2-*p*-toluene-sulphonyloxyethoxy)phenyl]-2-pyrimidine-amine (2.16g) and pyrrolidine (6.2ml, 75mmol) to give the title compound (680mg) as a yellow solid m.p. 154-155°. δH ($CDCl_3$) 12.0 (1H, br s), 8.25 (1H, br s), 8.03 (1H, d, J 5.7Hz), 7.73-7.72 (1H, m), 7.62-7.59 (1H, m), 7.53-7.50 (1H, m), 7.33 (1H, t, J 7.9Hz), 6.87 (2H, s), 6.29 (1H, d, J 5.7Hz), 4.53-4.47 (2H, br m), 3.90-3.80 (2H, br m), 3.79 (3H, s), 3.77 (3H, s), 3.49-3.42 (2H, br s), 3.08-3.00 (2H, br m), 2.25-2.10 (4H, br m).

The tosylate used as starting material was prepared from 4-(3-bromophenylsulphanyl)-N-[4,5-dimethoxy-3-(2-hydroxyethoxy)phenyl]-2-pyrimidine amine (1.80g, 3.76mmol) and *p*-toluenesulphonyl chloride (2.16g, 11.3mmol) in a manner similar to the analogous intermediate of Example 21 and was used without purification.

4-(3-Bromophenylsuphanyl)-N-[4,5-dimethoxy-3-(2-hydroxyethoxyphenyl)-2-pyrimidineamine was prepard in a manner similar to the intermediate of Example 19 as a buff solid. m.p. 151-152°. δH ($CDCl_3$) 8.07 (1H, d, J 5.4Hz), 7.75 (1H, t, J 1.8Hz), 7.61-7.50 (2H, m), 7.31 (1H, t, J 2.4Hz), 7.17 (1H, br s), 6.87 (1H, d, J 2.4Hz), 6.86 (1H, d, J 24.4Hz), 6.25 (1H, d, J 5.4Hz), 4.08-4.05 (2H, m), 3.91-3.88 (2H, m), 3.81 (3H, s), 3.80 (3H, s) and 2.70 (1H, br s).

EXAMPLE 29

4-(3-Bromophoenylsulphanyl)-N-[3-(N'-(S)-1-tert-butoxycarbonylprolyl)aminophenyl]-2-pyrimidineamine

In a manner similar to the preparation of the compound of Example 22, from the compound of Example 26 (1.0g, 2.68mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (514mg, 2.68mmol), hydroxyazabenzotriazole (402mg, 2.95mmol) N-methylmorpholine

(0.88ml,m 8.04mmol) and N-tert-butoxycarbonyl)-L-proline (635mg, 2.95mmol) to give the title compound (1.34g) as a white solid m.p. 135-137°. δH ($CDCl_3$) 9.40 (1H, br s), 8.08 (1H, d, J 5.4Hz), 7.77 (1H, t, J 1.8Hz), 7.64-7.60 (2H, m), 7.56-7.52 (1H, m), 7.35-7.22 (3H, m), 7.11-7.09 (2H, m), 6.37 (1H, d, J 5.4Hz), 4.43 (1H, br s), 3.42 (2H, br s), 2.50 (1H, br s), 2.00 (3H, br s) and 1.53 (9H, s).

EXAMPLE 30

4-(3-Bromophenylsulphanyl)-N-[3-(N'-(S)-prolyl)aminophenyl]-2-pyrimidineamine dihydrochloride

The compound of Example 29 (1.16, 2.02mmol) was dissolved in ethyl acetate (100ml) and dry hydrogen chloride gas was bubbled into the solution. After 10min a precipitate appeared which was collected and dried to give the title compound (890mg) as a yellow solid m.p. >175° (decomp). δH (d^6 DMSO) 10.73 (1H, s), 10.17 (1H, br m), 9.91 (1H, s), 8.64 (1H, br m), 8.22 (1H, d, J 5.4Hz), 7.87 (1H, t, J 1.8Hz), 7.81-7.77 (2H, m), 7.68-7.66 (1H, m), 7.50 (1H, t, J 7.9 Hz), 7.26-7.23 (2H, m), 7.07 (1H, t, J 8.1Hz), 6.49 (1H, d, J 5.4Hz), 6.07 (3H, br s), 4.40-4.37 (1H, br m), 3.30-3.20 (2H, br m, 2.43-2.38 (1H, m) and 1.97-1.86 (3H, br m).

EXAMPLE 31

N-(3,5-Dichloro-4-[(2-pyrrolidin-1-yl)ethoxy]phenyl}-4-(3,5-dimethylphenylsulphanyl)-2-pyrimidineamine

To a solution of N-(3,5-dichloro-4-hydroxyphenyl)-4-(3,5-dimethylphenyl-sulphanyl)-2-pyrimidineamine (1.0g, 2.55mmol - prepared from 4-amino-2,6-dichlorophenol and 2-chloro-4-(3,5-dimethylphenylsulphanyl)-pyrimidine according to the method of Example 4) in dry tetrahydrofuran were added triphenylphosphine (802mg, 3.06mmol) and N-(2-hydroxyethyl)pyrrolidine (0.3ml, 2.55mmol), followed by diethyl azadicarboxylate (0.49ml, 3.1mmol). The resulting solution was heated at reflux for 18h and on cooling the reaction was partitioned between ethyl acetate (200ml) and saturated aqueous $NaHCO_3$ (200ml). The organic phase was dried ($MgSO_4$), evaporated and the residue columned (silica; ethyl acetate) to give the title compound (400mg) as a white foam. δH 8.08 (1H, d, J 5.8Hz), 7.56 92H, s), 7.17 (2H, s), 7.09 (1H, s), 7.05 (1H, s), 6.28 (1H, d, J 5.8Hz), 4.18 (2H, t, J 8.6Hz), 2.59 (2H, t, J 8.6Hz), 2.59 (2H,

t, J 8.6Hz), 2.69 (4H, m), 2.31 (6H, s) and 1.80 (4H, m). MS m/z 489.2/490.9 (MH^+)

BIOLOGICAL ACTIVITY

The following assays were used to demonstrate the activity and selectivity of compounds according to the invention.

The activity of the compounds against src-family protein kinases can be determined in the following two assays:

$p56^{lck}$ kinase assay

The tyrosine kinase activity of $p56^{lck}$ was determined using a RR-src peptide (RRLIEDNEYTARG) and [γ-^{33}P]ATP as substrates. Quantitation of the ^{33}P-phosphorylated peptide formed by the action of $p56^{lck}$ was achieved using an adaption of the method of Geissler *et al* (J. Biol. Chem. (1990) 265, 22255-22261).

All assays were performed in 20mM HEPES pH 7.5 containing 10mM $MgCl_2$, 10mM $MnCl_2$, 0.05% Brij, 1μM ATP (0.5μCi[γ-^{33}P]ATP) and 0.8mg/ml RR-src. Inhibitors in dimethylsulphoxide (DMSO) were added such that the final concentration of DMSO did not exceed 1%, and enzyme [human $p56^{lck}$] such that the consumption of ATP was less than 10%. After incubation at 30°C for 15min, the reaction was terminated by the addition of one-third volume of stop reagent (0.25mM EDTA and 33mM ATP in dH_2O). A 15μl aliquot was removed, spotted onto a P-30 filtermat (Wallac, Milton Keynes, UK), and washed sequentially with 1% acetic acid and dH_2O to remove ATP. The bound ^{33}P-RR-src was quantitated by scintillation counting of the filtermat in a Betaplate scintillation counter (Wallac, Milton Keynes, UK) after addition of Meltilex scintillant (Wallac, Milton Keynes, UK). The dpm obtained, being directly proportional to the amount of ^{33}P-RR-src produced by $p56^{lck}$, were used to determine the IC_{50} for each compound.

In this assay the most potent compounds according to the invention have IC_{50} values of 100nM or less.

p59^{fyn} kinase assay

Compounds of the invention were assayed for p59^{fyn} inhibitory activity in a similar manner to the p56^{lck} assay, using human p59^{fyn}.

The selectivity of compounds according to the invention can be determined in an assay utilising a serine/threonine kinase:

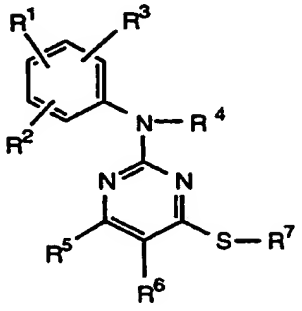
Protein kinase C assay

Inhibitor activity against protein kinase C (PKC) was determined using PKC obtained from Sigma Chemical Company (Poole, UK) and a commercially available assay system (Amersham International plc, Little Chalfont, UK). Briefly, PKC catalyses the transfer of the γ-phosphate (^{32}P) of ATP to the threonine group on a peptide specific for PKC. Phosphorylated peptide is bound go phosphocellulse paper, subsequently quantified by scintillation counting and IC_{50} values determined as described above.

In this assay, compounds according to the invention have IC_{50} values of 1μM and above.

CLAIMS

1. A compound of formula (1):



(1)

wherein R^1 is a $-XR^8$ group [where X is a covalent bond, -O-, -S-, -C(O)-, -C(S)-, -C(O)O-, -S(O)-, $-S(O_2)-$, $-CH_2-$, -or $N(R^9)-$ [where R^9 is a hydrogen atom or a straight or branched alkyl group] and R^8 is a hydrogen atom or an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group], or a $-NO_2$, -CN, $-SO_2NH_2$, $-SO_2NHR^8$, $-SO_2N(R^8)_2$ [where each R^8 group may be the same or different], $-CONH_2$, $-CONHR^8$, $-CON(R^8)_2$ [where each R^8 group may be the same or different], $-CSNH_2$, $-CSNHR^8$, $-CSN(R^8)_2$ [where each R^8 group may be the same or different], $-NH_2$ or substituted amino group;

R^2 and R^3 which may be the same or different is each a hydrogen or halogen atom or a group selected from an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, -OH, $-OR^{10}$ [where R^{10} is an optionally substituted aliphatic group], $-OR^{10a}$ [where R^{10a} is an optionally substituted cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group] -SH, $-NO_2$, -CN, $-SR^8$, $-COR^8$, $S(O)R^8$, $-SO_2R^8$, $-SO_2NH_2$, $-SO_2NHR^8$, $-SO_2N(R^8)_2$ [where each R^8 group may be the same or different] $-CO_2H$, $-CO_2R^8$, $-CONH_2$, - $CONHR^8$, $-CON(R^8)_2$, [where each R^8 group may be the same or different] $-CSNH_2$, $-CSNHR^8$, $-CSN(R^8)_2$, [where each R^8 group may be the same or different] $-NH_2$ or substituted amino group provided that when one or both of

R^2 and R^3 is an $-OR^{10}$ group then R^1 is an $-OR^8$ group in which R^8 is an optionally substituted cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group or an aliphatic group substituted by a cyclic amino group;

R^4 is a hydrogen atom or a straight or branched alkyl group;

R^5 is a hydrogen atom or an optionally substituted straight or branched alkyl, alkenyl or alkynyl group;

R^6 is a hydrogen or halogen atom or an amino, substituted amino, nitro, $-CO_2H$, or $-CO_2R^8$ group or a group $-X^1-R^{6a}$ where X^1 is a direct bond or a linker atom or group and R^{6a} is an optionally substituted straight or branched alkyl, alkenyl or alkynyl group;

R^7 is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group; and the salts, solvates, hydrates and N-oxides thereof.

2. A compound according to Claim 1 in which R^4, R^5 and R^6 is each a hydrogen atom.

3. A compound according to Claim 1 or Claim 2 in which R^7 is an optionally substituted aromatic or heteroaromatic group.

4. A compound according to Claim 3 in which R^7 is an optionally substituted phenyl, 1- or 2-naphthyl, pyrrolyl, furyl, thienyl, indolyl, pyrazolyl, thiazolyl, [2,3-dihydro]benzofuryl, benzothiazolyl, 2-pyridyl, 3-pyridyl or 4-pyridyl group.

5. A compound according to any one of Claims 1 to 4 in which R^1 is attached at the3- position of the phenyl ring R^2 and R^3 are attached at the 4- and 5- positions or R^1 is attached at the 4- position and R^2 and R^3 are attached at the 3- and 5- positions.

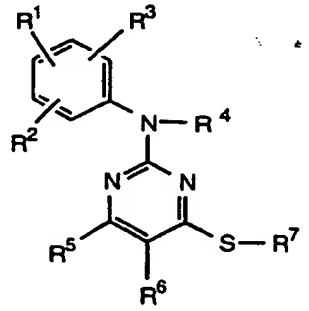
6. A compound according to Claim 5 in which R^1 is a $-R^8$ or $-OR^8$ group.

7. A compound according to Claim 6 in which R^1 is an optionally substituted heterocycloaliphatic or alkoxy group.

8. A compound according to any one of Claims 1 to 7 in which R^2 or R^3 is each a hydrogen atom or a methyl or methoxy group.

9. A compound which is:
4-(3-methoxyphenylsulphanyl)-N-{[3,5-dimethyl-4-(2-(pyrrolidin-1-yl)-ethoxy]phenyl}-2-pyrimidineamine ;
4-(3-Carboxyphenylsuphanyl)-N-{[3,5-dimethyl-4-(2-pyrrolidin-1-yl)-ethoxy]phenyl}-2-pyrimidineamine;
N-[4,5-Dimethoxy-3-(2-pyrrolidin-1-ylethoxy)]-4-(3-methoxyphenyl-sulphanyl)-2-pyrimidineamine;
4-(3-Methoxyphenylsulphanyl)-N-{4-methoxy-[3-(2-pyrrolidin-1-yl)-ethoxy]phenyl}2-pyrimidineamine;
N-{3,5-Dimethoxy-4-[2-(pyrrolidin-1-yl)ethoxy]phenyl}-4-(3-methoxy-phenylsulphanyl)-2-pyrimidineamine;
N-{[4,5-Dimethoxy-3-(2-pyrrolin-1-yl)ethoxy]phenyl}-4-(4-fluorophenyl-sulphanyl) pyrimidine-2-amine;
4-(3-Bromophenylsulphanyl)-N-[4,5-dimethoxy-3-(2-pyrrolidin-1-yl-ethoxy)phenyl]-2-pyrimidineamine;
N-{3,5-Dichloro-4-[(2-pyrrolidin-1-yl)ethoxy]phenyl}-4-(3,5-dimethyl-phenylsulphanyl)-2-pyrimidineamine;
and the salts, solvates and hydrates thereof.

10. A pharmaceutical composition comprising a compound of formula (1):



(1)

wherein R^1 is a $-XR^8$ group [where X is a covalent bond, -O-, -S-, -C(O)-, -C(S)-, -C(O)O-, -S(O)-, $-S(O_2)-$, $-CH_2-$, -or $N(R^9)-$ [where R^9 is a hydrogen atom or a straight or branched alkyl group] and R^8 is a hydrogen atom or an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group], or a $-NO_2$, -CN, $-SO_2NH_2$, $-SO_2NHR^8$, $-SO_2N(R^8)_2$ [where each R^8 group may be the same or different], $-CONH_2$, $-CONHR^8$, $-CON(R^8)_2$ [where each R^8 group may be the same or different], $-CSNH_2$, $-CSNHR^8$, $-CSN(R^8)_2$ [where each R^8 group may be the same or different], $-NH_2$ or substituted amino group;

R^2 and R^3 which may be the same or different is each a hydrogen or halogen atom or a group selected from an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, -OH, $-OR^{10}$ [where R^{10} is an optionally substituted aliphatic group], $-OR^{10a}$ [where R^{10a} is an optionally substituted cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group] -SH, $-NO_2$, -CN, $-SR^8$, $-COR^8$, $S(O)R^8$, $-SO_2R^8$, $-SO_2NH_2$, $-SO_2NHR^8$, $-SO_2N(R^8)_2$ [where each R^8 group may be the same or different] $-CO_2H$, $-CO_2R^8$, $-CONH_2$, - $CONHR^8$, $-CON(R^8)_2$, [where each R^8 group may be the same or different] $-CSNH_2$, $-CSNHR^8$, $-CSN(R^8)_2$, [where each R^8 group may be the same or different] $-NH_2$ or substituted amino group provided that when one or both of R^2 and R^3 is an $-OR^{10}$ group then R^1 is an $-OR^8$ group in which R^8 is an optionally substituted cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group or an aliphatic group substituted by a cyclic amino group;

R^4 is a hydrogen atom or a straight or branched alkyl group;

R^5 is a hydrogen atom or an optionally substituted straight or branched alkyl, alkenyl or alkynyl group;

R^6 is a hydrogen or halogen atom or an amino, substituted amino, nitro, $-CO_2H$, or $-CO_2R^8$ group or a group $-X^1-R^{6a}$ where X^1 is a direct bond or a linker atom or group and R^{6a} is an optionally substituted straight or branched alkyl, alkenyl or alkynyl group;

R^7 is an optionally substituted aliphatic, cycloaliphatic, heteroaliphatic, heterocycloaliphatic, aromatic or heteroaromatic group; and the salts, solvates, hydrates and N-oxides thereof; together with one or more pharmaceutically acceptable carriers, excipients or diluents.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB 98/00767

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/46 C07D401/12 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 264 348 A (CIBA-GEIGY) 20 April 1988 see claims; tables 1,2	1
A	EP 0 172 786 A (CIBA-GEIGY) 26 February 1986 see claims; table 1	1
A	EP 0 135 472 A (CIBA-GEIGY) 27 March 1985 see claims; tables 1,4	1
P,X	WO 97 19065 A (CELLTECH THERAPEUTICS) 29 May 1997 see page 71 - page 80; example 139	1,10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 June 1998	16/06/1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

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INTERNATIONAL SEARCH REPORT

Information on patent family members

l: ational Application No
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